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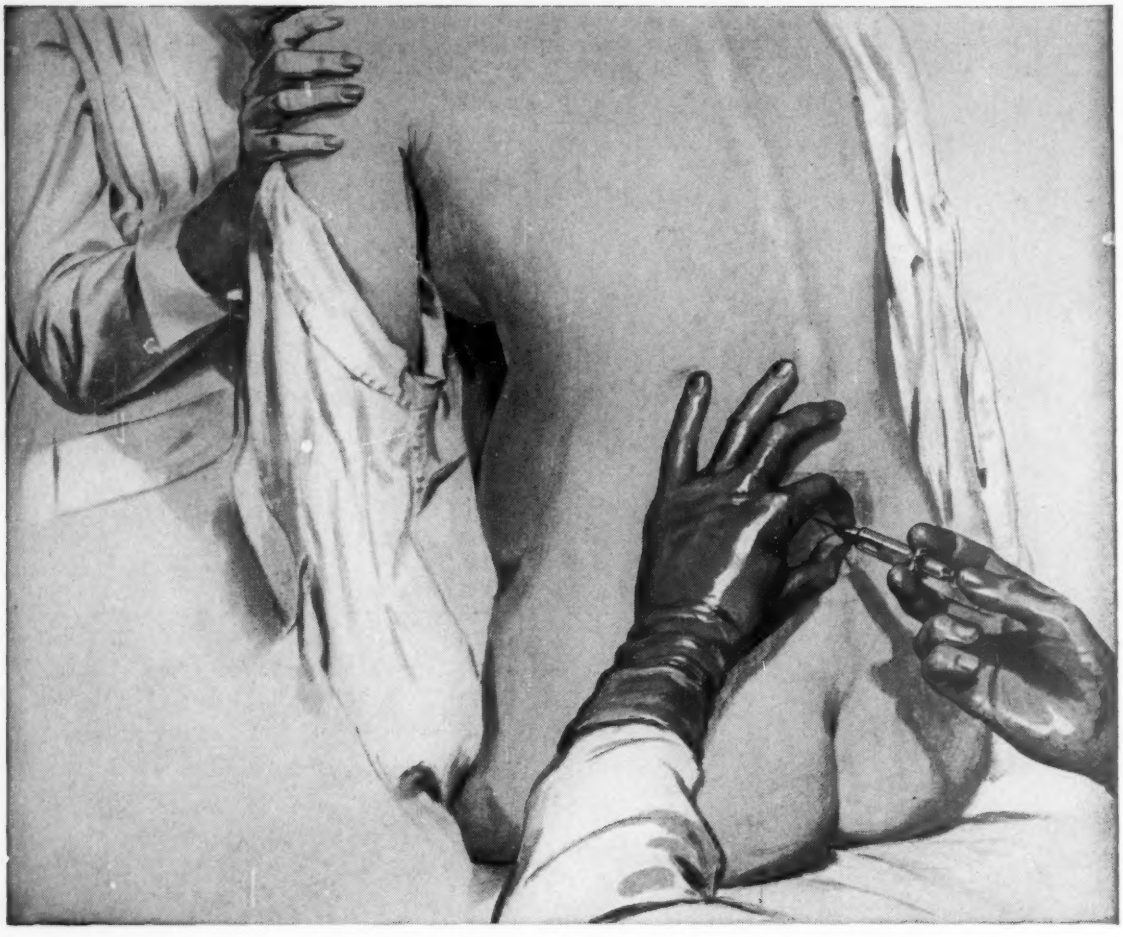

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CONTENTS

for February, 1958

GYNECOLOGY

Endometrium

THE RELATION OF NONMALIGNANT POSTMENOPAUSAL ENDOMETRIAL CHANGES TO OVARIAN MORPHOLOGY
J. W. Roddick, Jr., M.D., and R. R. Greene, M.D., Chicago, Ill. 235

CYCLICAL CHANGES OF ELECTROLYTES IN ENDOMETRIAL TISSUE
Theodore H. Johnson, A.B., New York, N. Y. 240

EXPERIMENTAL METAPLASIA OF THE ENDOMETRIUM
E. Momigliano, M.D., Chicago, Ill. 249

Endometriosis

CONCURRENT AND INTERRELATED STROMAL ENDOMETRIOSIS (STROMATOSIS; STROMAL SARCOMA) AND UTERINE ADENOMYOSIS
Warren C. Hunter, M.D., Portland, Ore., and Gerald J. Lattig, M.D., Everett, Wash. 258

THE USE OF NEWER PROGESTINS IN THE TREATMENT OF ENDOMETRIOSIS
Robert W. Kistner, M.D., Brookline, Mass. 264

INGUINAL ENDOMETRIOSIS
Kenneth R. Niswander, M.D., Buffalo, N. Y. 279

ADENOCARCINOMA OF THE OVARY WITH PROBABLE ORIGIN IN ENDOMETRIAL CYST
C. A. Stern, M.D., Sioux Falls, S. D. 282

OVARIAN PREGNANCY AND ENDOMETRIOSIS
John R. Durburg, M.D., and Hugh Gavin Grimes, M.D., Chicago, Ill. 285

Endocrines

PROGESTATIONAL AND ANDROGENIC SUBSTANCES TESTED ON THE HIGHLY PROLIFERATED VAGINAL EPITHELIUM OF SURGICAL CASTRATES. II. ANDROGENIC SUBSTANCES
George L. Wied, M.D., Jose R. del Sol, M.D., and Alice M. Dargan, M.A., Chicago, Ill. 289

INDUCTION OF OVULATION IN THE HUMAN: THERAPEUTIC AND DIAGNOSTIC IMPORTANCE
Herbert S. Kupperman, M.D., Jeanne A. Epstein, M.D., Meyer H. G. Blatt, M.D., and Abraham Stone, M.D., New York, N. Y. 301

contents...

continued from page 1

Vagina and Vulva

HIDRADENOMA OF THE VULVA
Joseph T. Chung, M.D., and R. R. Greene, M.D., Chicago, Ill. 310

LOCAL HYDROCORTISONE THERAPY OF VAGINAL AND VULVAL PRURITUS
Rita S. Finkler, M.D., Newark, N. J. 319

MAINTENANCE OF TRICHOMONAS VAGINALIS IN SIMPLIFIED TRYPTICASE SERUM MEDIUM WITHOUT MALTOSE
Louis G. Feo, M.D., Philadelphia, Pa. 322

GRANULAR-CELL MYOBLASTOMA OF THE VULVA
Lawrence B. Winkelstein, M.D., and Stanley Friedman, M.D., Mount Vernon, N. Y. 325

Radiation Hazards

RADIATION HAZARDS IN OBSTETRICS AND GYNECOLOGY
Stephen S. Parlee, M.D., Edmonton, Alberta 327

Surgical Techniques

TECHNIQUES OF ABDOMINAL TOTAL HYSTERECTOMY, WITH REPORT OF THREE METHODS USED IN 1,000 CASES
Laman A. Gray, M.D., Louisville, Ky. 334

OBSTETRICS

Erythroblastosis and Blood Group Incompatibility

THE OUTLOOK FOR FUTURE PREGNANCIES IN WOMEN IMMUNIZED TO RH
Edith L. Potter, M.D., Chicago, Ill. 348

THE DIAGNOSIS AND TREATMENT OF ERYTHROBLASTOSIS FETALIS
Mila Pierce, M.D., Eustacia Rigor, M.D., and Abbie Luken, Chicago, Ill. 357

CLINICAL VALUE OF SEROLOGIC EXAMINATIONS RELATED TO BLOOD GROUPS IN PREGNANT PATIENTS
Kurt Stern, M.D., Chicago, Ill. 369

Cesarean Section

FACTORS INFLUENCING PERINATAL MORTALITY IN CESAREAN SECTION
Orvan W. Hess, M.D., New Haven, Conn. 376

CURRENT ASPECTS OF CESAREAN SECTION AND PERINATAL MORTALITY
J. Edward Hall, M.D., Schuyler G. Kohl, M.D., and H. R. Schechter, B.S., Brooklyn, N. Y. 387

TOTAL HYSTERECTOMY FOR STERILIZATION FOLLOWING CESAREAN SECTION
Jack G. Hallatt, M.D., and Henry Hirsch, M.D., Los Angeles, Calif. 396

VAGINAL DELIVERY FOLLOWING CESAREAN SECTION
Harold M. Jesurun, Lieutenant Colonel, MC, USA, and John W. Simpson, Colonel, MC, USA 401

(Contents continued on Page 4)

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contents . . .

continued from page 2

Hypofibrinogenemia

HYPOFIBRINOGENEMIA AND THE PLACENTA
James G. Stouffer, M.D., and Charles T. Ashworth, M.D., Fort Worth, Texas . 407

FIBRINOLYTIC FIBRINOGENOPENIA
Jessica H. Lewis, M.D., Deborah C. Leary, M.D., James W. Fresh, B.S., and John H. Ferguson, M.D., Chapel Hill, N. C. 418

Physical Aids

A WARM AIR BLOWER FOR PERINEAL WOUNDS
Virgil S. Counseller, M.D., and John S. Welch, M.D., Rochester, Minn. . . . 423

DISPOSABLE CORD CLAMP THAT ESTABLISHES UNMISTAKABLE IDENTIFICATION OF THE NEWBORN
J. Bay Jacobs, M.D., Washington, D. C. 425

BANDING THE UMBILICAL CORD
York Lancaster, M.D., Port Lavaca, Texas 428

A NEW FETOSCOPE ATTACHMENT
A. Perell, M.D., Summit, N. J. 430

A MODIFIED RECEPTOR FOR EXTERNAL TOKODYNAMOMETRY
Paul E. Stroup, M.D., and S. Leon Israel, M.D., Philadelphia, Pa. 431

Toxemia of Pregnancy

PROTOVERATRINE IN TOXEMIA OF PREGNANCY
Edward G. Winkler, M.D., and Vincent W. Cangello, M.D., Buffalo, N. Y. . . . 433

THE PATHO-MECHANISM OF LATE PREGNANCY TOXEMIA AND OBSTETRICAL HEMORRHAGES. I. CONTRADICTION IN THE CLINICAL PICTURES OF ECLAMPSIA AND PLACENTA PREVIA DEPENDING UPON THE PLACENTAL SITE
J. Bieniarz, M.D., Gdańsk, Poland 444

PREFRONTAL LOBOTOMY AND SEVERE PRE-ECLAMPSIA
Samuel J. Turner, M.D., Chicago, Ill. 454

EDITORIAL

APPOINTMENT OF NEW EDITORS
Howard C. Taylor, Jr. 457

REVIEWS AND ABSTRACTS

REVIEWS OF NEW BOOKS 458
BOOKS RECEIVED FOR REVIEW 460
SELECTED ABSTRACTS 460

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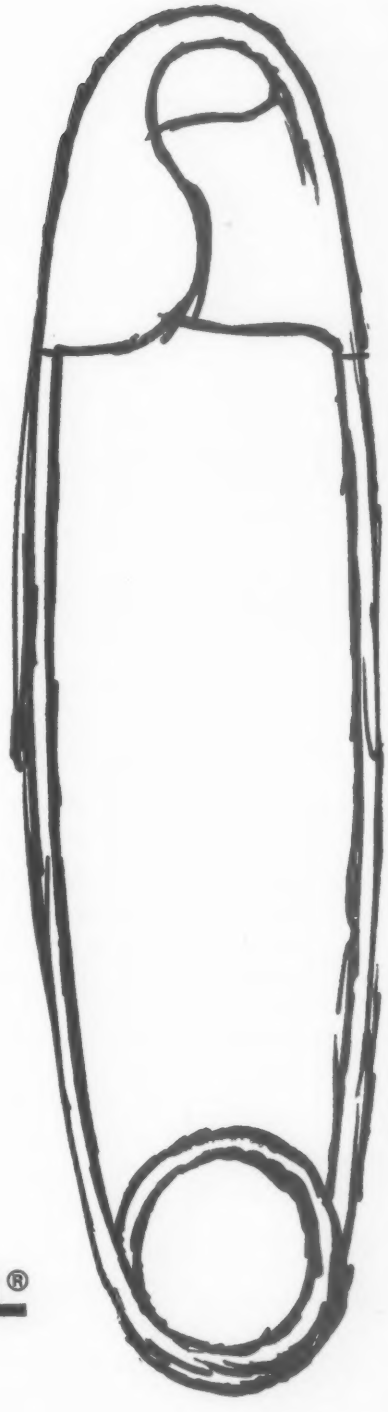

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1. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. *14*:531 (May) 1954. **2.** Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. *15*:206 (Jan.) 1955. **3.** Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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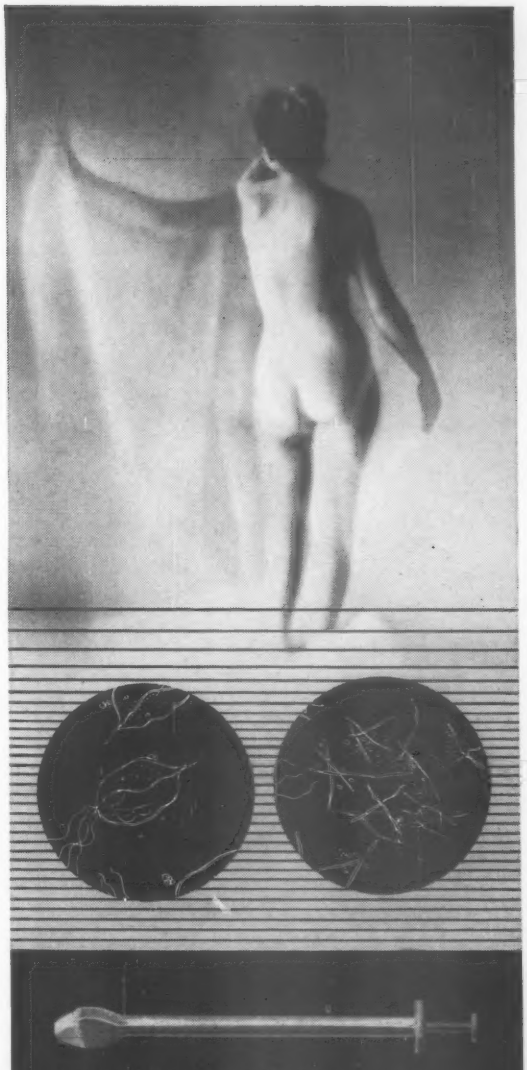
1. Gardner, H. L.; Dampeer, T. K., and Dukes, C. D.: The Prevalence of Vaginitis, A Study in Incidence, Am. J. Obst. and Gynec. *73*:1080 (May) 1957.
2. Williamson, P.: Trichomonad Infestation, M. Times *84*:929 (Sept.) 1956.
3. Lang, W. R.: Recent Advances in Vaginitis, Philadelphia Med. *51*:1494 (June 15) 1956.



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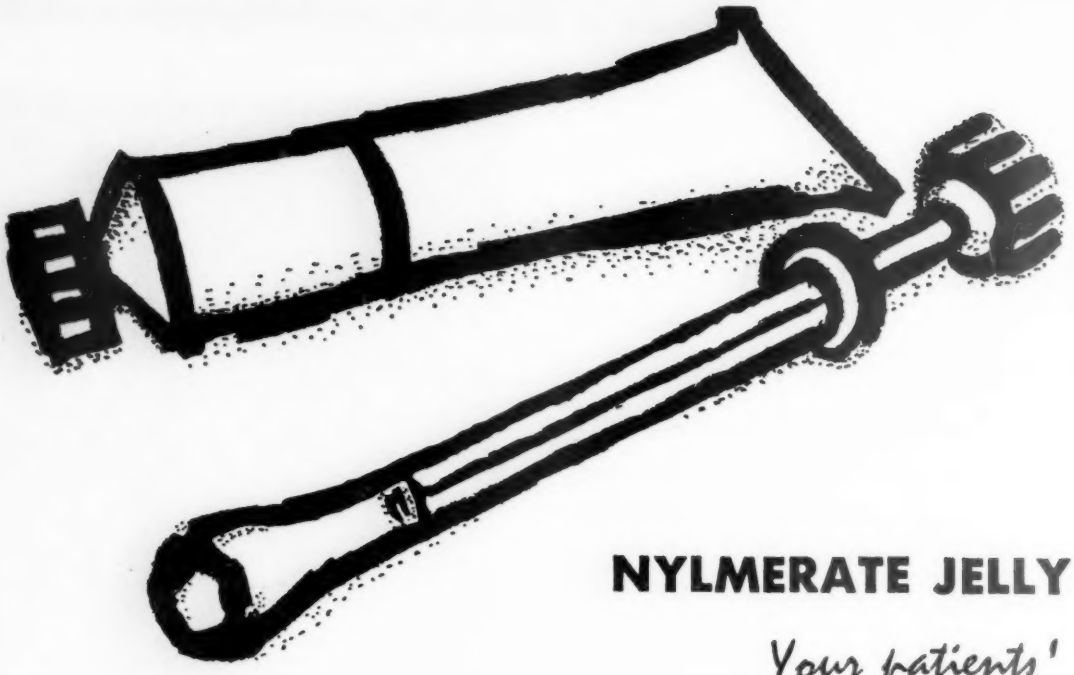

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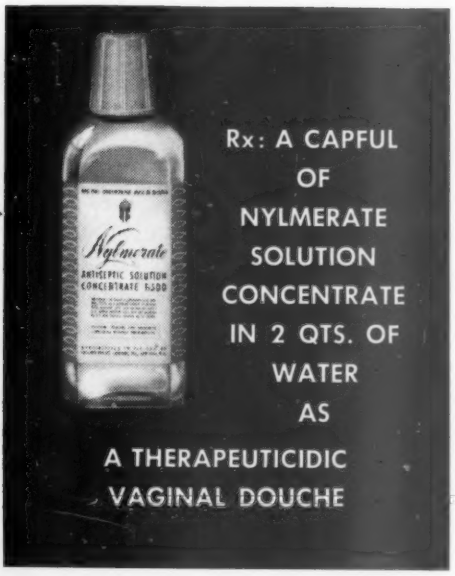

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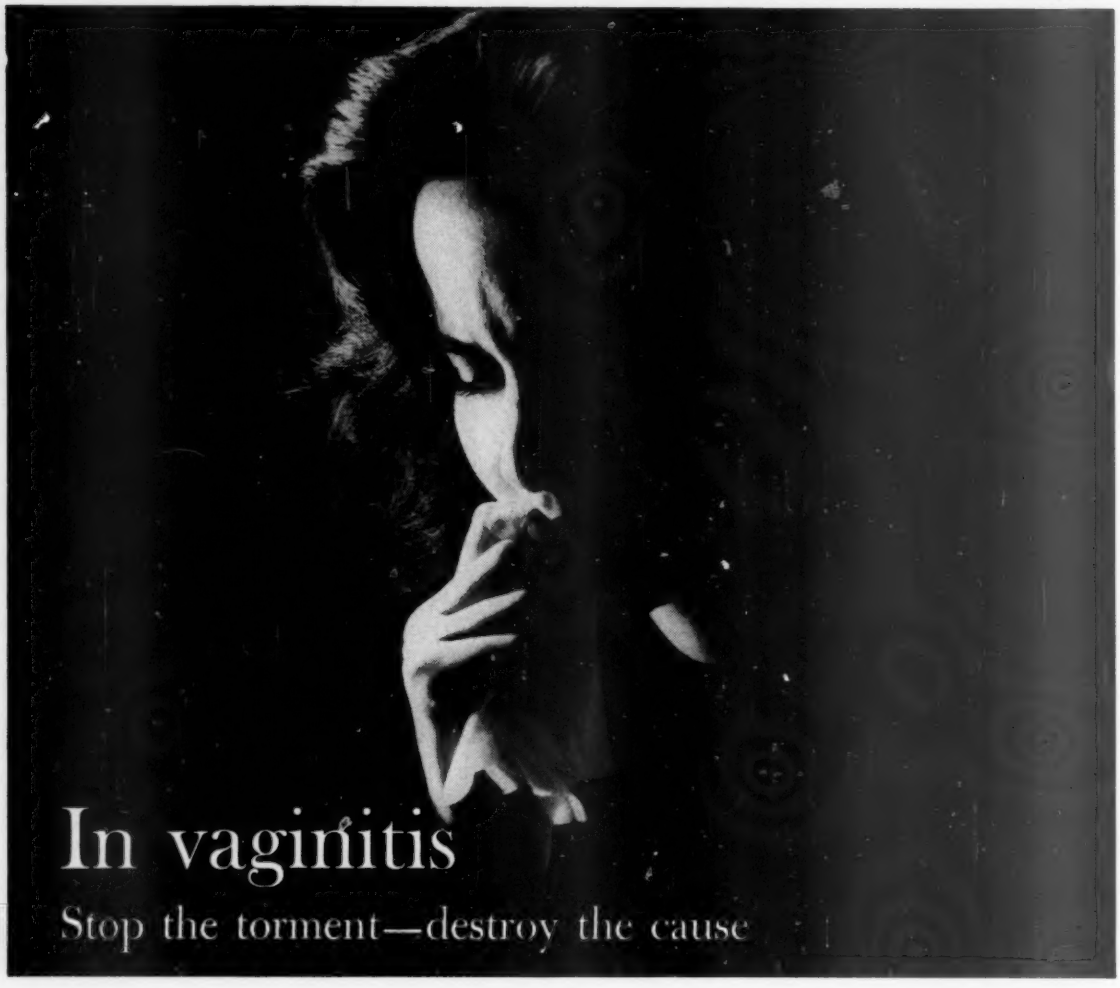

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(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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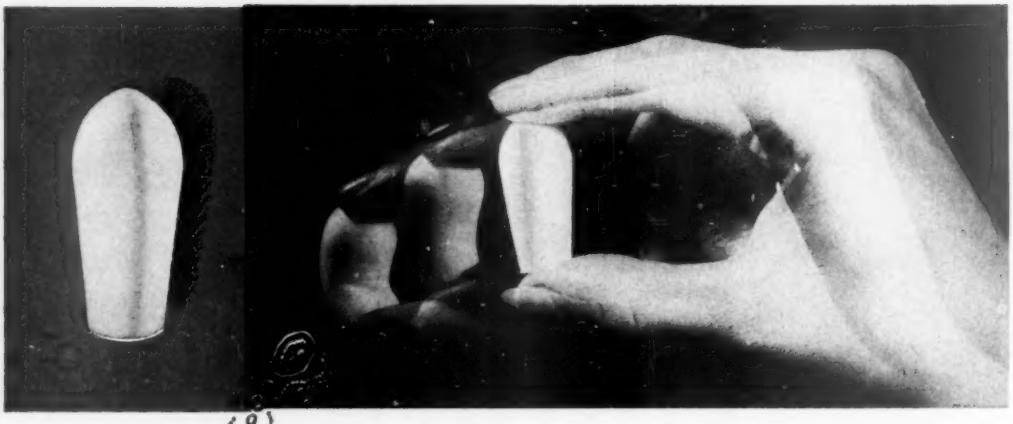

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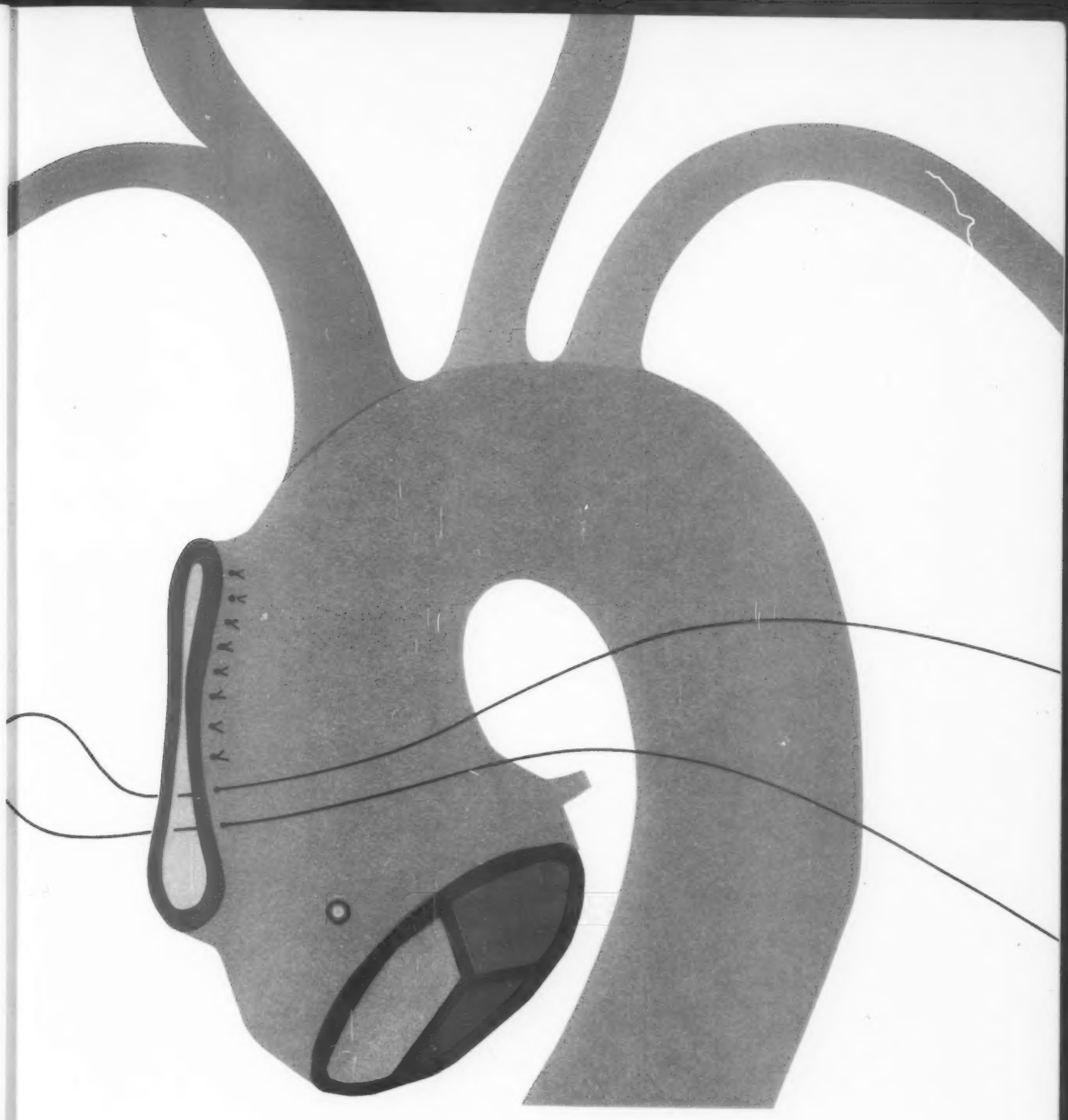

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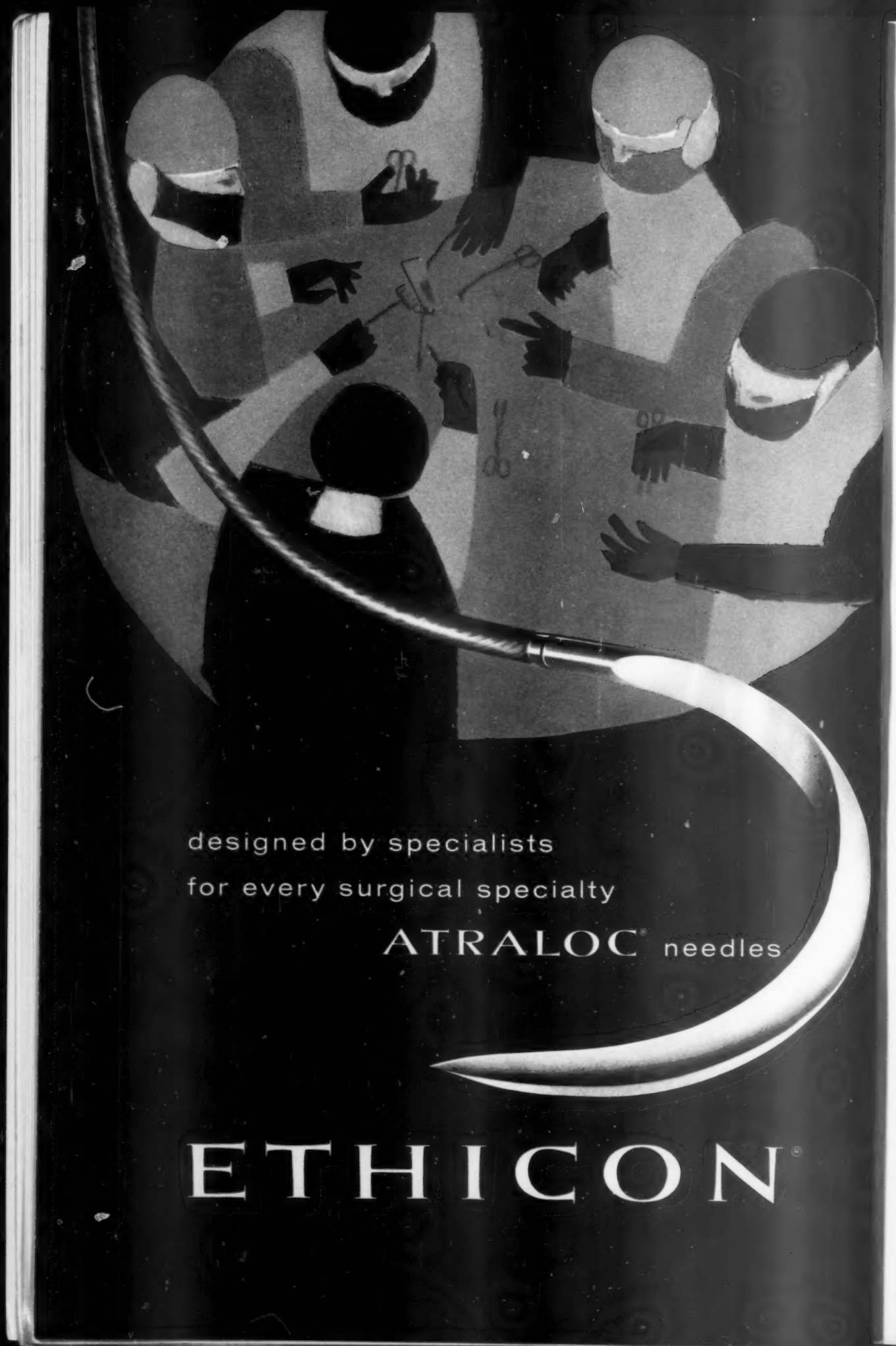
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BIBLIOGRAPHY: (1) Hagedorn, A. B.: J.A.M.A. *164*:1642 (Aug. 10) 1957. (2) Brown, E. B., and Moore, C. V., in Tocantins, L. M.: Progress in Hematology, New York, Grune & Stratton, Inc., 1956, vol. 1, p. 25. (3) Hagedorn, A. B.: M. Clin. North America, Philadelphia, W. B. Saunders Company (July) 1956, p. 983. (4) Grunberg, A., and Blair, J. L.: A.M.A. Arch. Int. Med. *96*:731, 1955. (5) Baird, I. M., and Podmore, D. A.: Lancet *2*:942 (Nov. 6) 1954. (6) Cappell, D. F.; Hutchison, H. E.; Hendry, E. B., and Conway, H.: Brit. M. J. *2*:1255 (Nov. 27) 1954. (7) Millard, J. B., and Barber, H. S.: Ann. Rheumat. Dis. *15*:51, 1956. (8) Cope, E.; Gillhespy, R. O., and Richardson, R. W.: Brit. M. J. *2*:639 (Sept. 15) 1956. (9) Jennison, R. F., and Ellis, H. R.: Lancet *2*:1245 (Dec. 18) 1954. (10) Scott, J. M., and Govan, A. D. T.: Brit. M. J. *2*:1257 (Nov. 27) 1954. (11) Scott, J. M.: Brit. M. J. *2*:635 (Sept. 15) 1956. (12) Gaisford, W., and Jennison, R. F.: Brit. M. J. *2*:700 (Sept. 17) 1955. (13) Wallerstein, R. O., and Hoag, M. S.: Scientific Exhibit, Sixth Internat. Cong., Internat. Soc. Hemat., Boston, Mass., Aug. 27-Sept. 1, 1956. (14) Wallerstein, R. O.: J. Pediat. *49*:173, 1956. (15) Sturgeon, P.: Pediatrics *18*:267, 1956. (16) Wallerstein, R. O., and Hoag, M. S.: J.A.M.A. *164*:962 (June 29) 1957.

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IN PRENATAL NUTRITION
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IN the diet planned to reduce obesity it appears especially important that the total allowed calorie intake be well distributed over the day's customary three meals. A ratio of approximately 25% of the day's calories at breakfast, 35% at luncheon, and 40% at dinner has found wide acceptance.

Thus a sensible reducing regimen begins with a sensible breakfast—one which contributes a reasonable share of the day's total requirement of all essential nutrients, provides approximately one-fourth of the day's calories, and prevents undue hunger and helps maintain acuity during the morning hours.

A bowl of steaming oatmeal (¾ cup cooked oatmeal, 4 ounces skim milk, and 1 level teaspoon sugar) fits well into such a breakfast, whether the total calorie allowance be 1000, 1200, or 1600 calories per day.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

NUTRIENT CONTENT OF THE OATMEAL BREAKFAST SERVING

(¾ cup cooked oatmeal, 4 ounces skim milk, and 1 level teaspoon sugar)
Approximately 170 calories

Protein	9.0 Gm.	Folic acid	11.7 mcg.
Carbohydrate	28.0 Gm.	Iron	1.38 mg.
Fat	2.1 Gm.	Calcium	167 mg.
Thiamine	0.23 mg.	Phosphorus	235 mg.
Niacin	0.41 mg.	Potassium	325 mg.
Riboflavin	0.27 mg.	Zinc	1.53 mg.
Pyridoxine	0.13 mg.	Copper	0.35 mg.
Pantothenic acid	0.66 mg.	Manganese	1.45 mg.
Vitamin B_{12}	0.8 mcg.	Magnesium	65 mg.

A 300 calorie breakfast of 4 ounces of orange juice, the serving of oatmeal, a slice of lightly buttered toast, and coffee or tea (with artificial sweetener, if desired) is a sensible, satisfying, and nutritious morning meal in the reducing regimen.

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157 patients showed negative culture tests at 3 months follow-up examinations. Patients reported rapid relief of burning and itching, often within 24 hours.

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STEP 2 *Home* use of TRICOFURON VAGINAL SUPPOSITORIES [redacted] by the patient, 1 or 2 daily, including the important menstrual days.

*Combined results of 12 independent clinical investigators. Data available on request.

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0.375% Micofur, 0.25% Furoxone.

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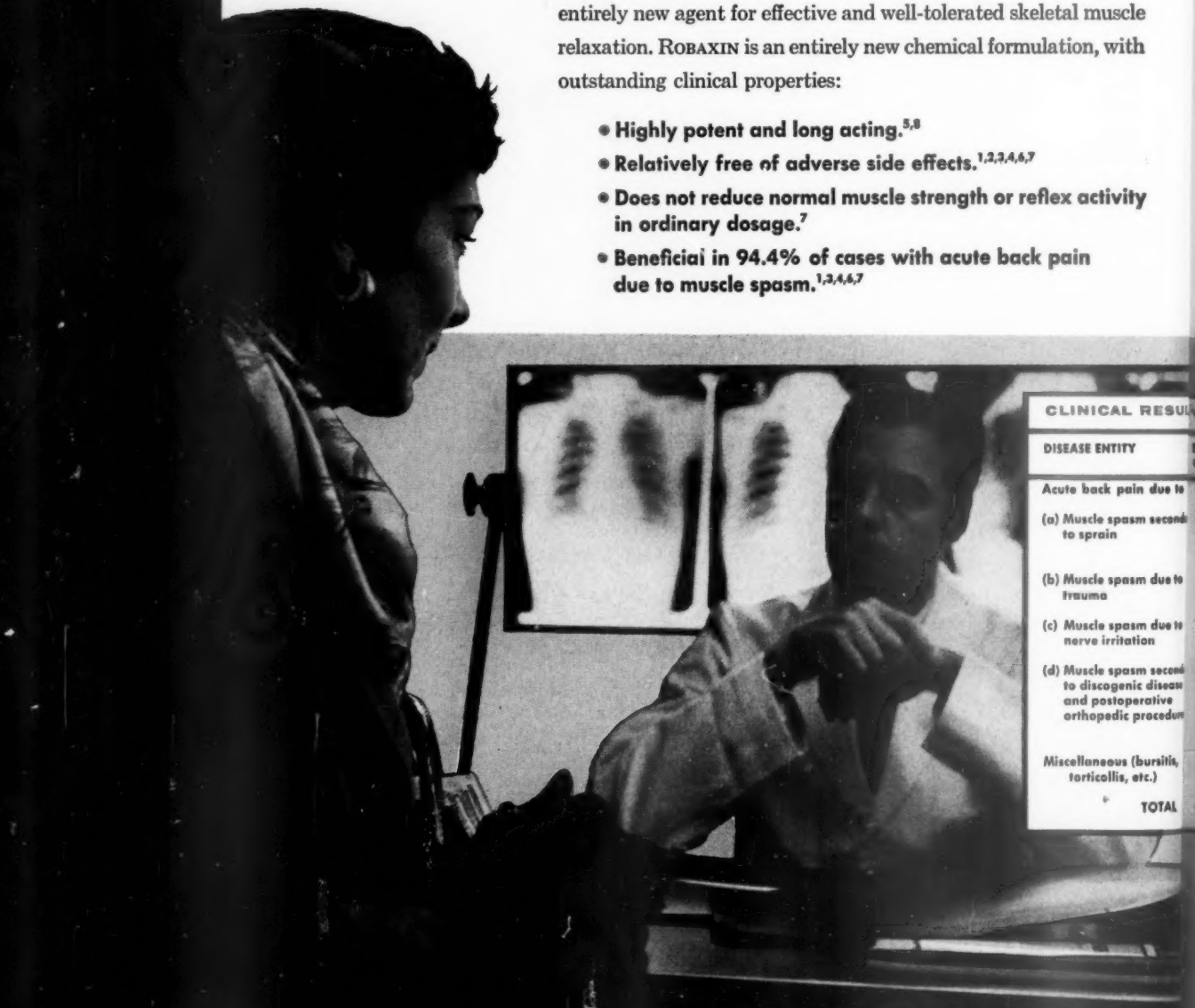
- **Highly potent and long acting.**[5,8]
- **Relatively free of adverse side effects.**[1,2,3,4,6,7]
- **Does not reduce normal muscle strength or reflex activity in ordinary dosage.**[7]
- **Beneficial in 94.4% of cases with acute back pain due to muscle spasm.**[1,3,4,6,7]



CLINICAL RESUL WITH ROB

DISEASE ENTITY	NO. OF CASES	DURA O TREAT
Acute back pain due to		
(a) Muscle spasm secondi to sprain	18	2-42
(b) Muscle spasm due to trauma	13	1-42
(c) Muscle spasm due to nerve irritation	5	4-240
(d) Muscle spasm second to discogenic disease and postoperative orthopedic procedure	30	2-28
Miscellaneous (bursitis, torticollis, etc.)	6	3-60
TOTAL	72	

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(Methocarbamol Robins, U.S. Pat. No. 2770649)

Highly specific action

ROBAXIN is highly specific in its action on the internuncial neurons of the spinal cord – with inherently sustained repression of multisynaptic reflexes, but with no demonstrable effect on monosynaptic reflexes. It thus is useful in the control of skeletal muscle spasm, tremor and other manifestations of hyperactivity, as well as the pain incident to spasm, without impairing strength or normal neuromuscular function.

Beneficial in 94.4% of cases tested

When tested in 72 patients with acute back pain involving muscle spasm, ROBAXIN induced marked relief in 59, moderate relief in 6, and slight relief in 3 – or an over-all beneficial effect in 94.4%.[1,3,4,6,7] No side effects occurred in 64 of the patients, and only slight side effects in 8. In studies of 129 patients, moderate or negligible side effects occurred in only 6.2%.[1,2,3,4,6,7]

RESULTS WITH ROBAXIN IN ACUTE BACK PAIN[1,2,4,6,7]

	NO. OF CASES	DURATION OF TREATMENT	DOSE PER DAY (divided)	RESPONSE marked	mod.	slight	neg	SIDE EFFECTS
in due to								
sm second	18	2-42 days	3-6 Gm.	17	1	0	0	None, 16 Dizziness, 1 Slight nausea, 1
sm due to	13	1-42 days	2-6 Gm.	8	1	3	1	None, 12 Nervousness, 1
sm due to tion	5	4-240 days	2.25-6 Gm.	4	1	0	0	None, 5
sm second nic disease perative procedure	30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25 Dizziness, 1 Lightheadedness, 2 Nausea, 2 *
(bursitis, , etc.)	6	3-60 days	4-8 Gm.	6	0	0	0	None, 6
TOTAL	72			59	6	3	4	*Relieved on reduction of dose

References: 1. Carpenter, E. B.: Publication pending. 2. Carter, C. H.: Personal communication. 3. Forsyth, H. F.: Publication pending. 4. Freund, J.: Personal communication. 5. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: American Pharm. Assn. 46:374, 1957. 6. Nachman, H. M.: Personal communication. 7. O'Doherty, D.: Publication pending. 8. Truitt, E. B., Jr., and Little, J. M.: J. Pharm. & Exper. Therap. 119:161, 1957.

Indications – Acute back pain associated with: (a) muscle spasm secondary to sprain; (b) muscle spasm due to trauma; (c) muscle spasm due to nerve irritation; (d) muscle spasm secondary to discogenic disease and postoperative orthopedic procedures; and miscellaneous conditions, such as bursitis, fibrositis, torticollis, etc.

Dosage – Adults: Two tablets 4 times daily to 3 tablets every 4 hours. Total daily dosage: 4 to 9 Gm. in divided doses.

Precautions – There are no specific contraindications to Robaxin and untoward reactions are not to be anticipated. Minor side effects such as lightheadedness, dizziness, nausea may occur rarely in patients with unusual sensitivity to drugs, but disappear on reduction of dosage. When therapy is prolonged routine white blood cell counts should be made since some decrease was noted in 3 patients out of a group of 72 who had received the drug for periods of 30 days or longer.

Supply – Robaxin Tablets, 0.5 Gm., in bottles of 50.

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Dysfunctional uterine bleeding
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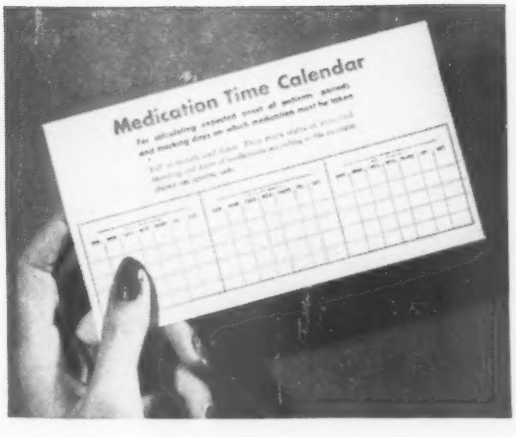
1. Amer. J. Obst. & Gynec., 68:1321, 1954.



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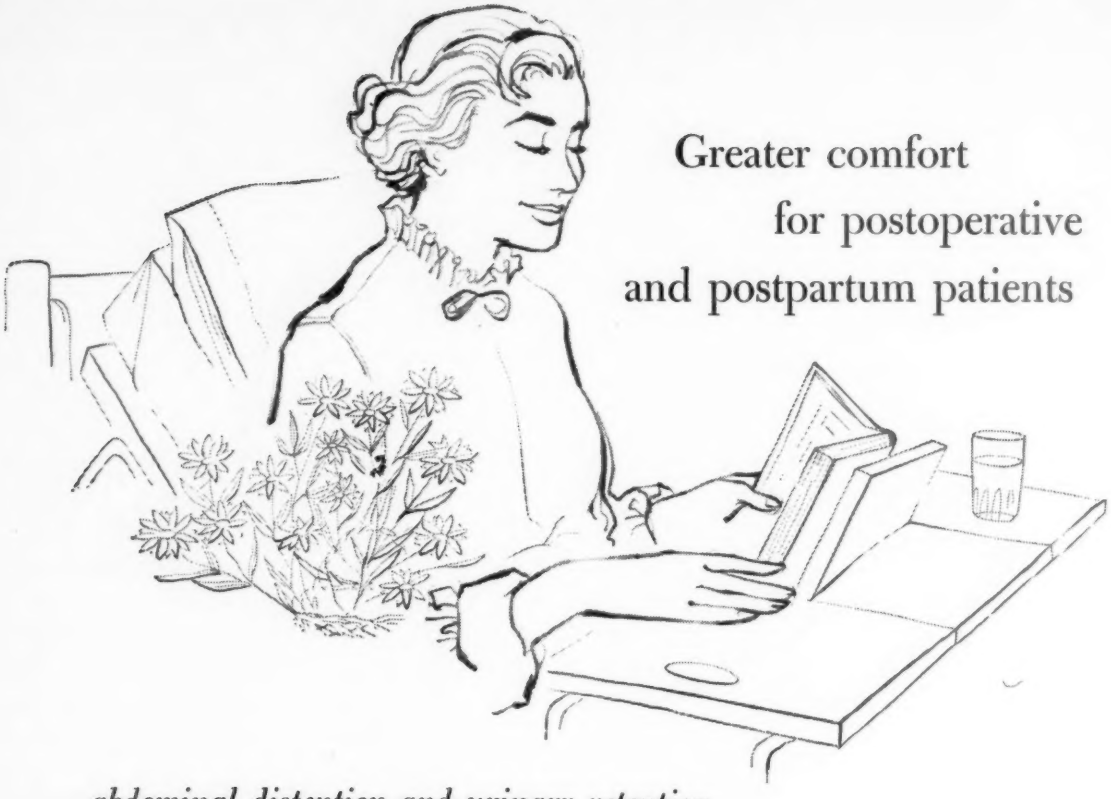

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abdominal distention and urinary retention
can often be prevented or promptly relieved
– with less need for uncomfortable enemas and catheters

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Administration and dosage: may be given prophylactically or therapeutically after surgery or childbirth. Usual oral dosage: 10 to 30 mg. three or four times daily. Usual subcutaneous dosage: 5 mg. three or four times daily.

Other indications: gastric atony and retention following vagotomy and other surgical procedures; chronic functional urinary retention due to atony without obstruction; megacolon, including congenital megacolon (Hirschsprung's disease); certain cases of paralytic ileus; to counteract side effects of antihypertensive ganglionic blocking drugs.

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to control oozing and bleeding

As one clinician states: "Blood loss may be hidden temporarily after closure of the thoracic or abdominal cavities, even though drains are in place. Obstruction to outflow through these drains can occur, and bleeding is not apparent.

"There are certain clinical situations in which prolonged and profound oozing of blood may occur."[1]

Published reports[2-6] over the last five years emphasize the value of Adrenosem preoperatively—to control oozing and bleeding and provide a clearer operative field.

Adrenosem does not affect blood pressure, cardiac rate or output, blood clotting mechanism, massive hemorrhage, or arterial bleeding.[7]

Supplied in ampuls, tablets and as a syrup.

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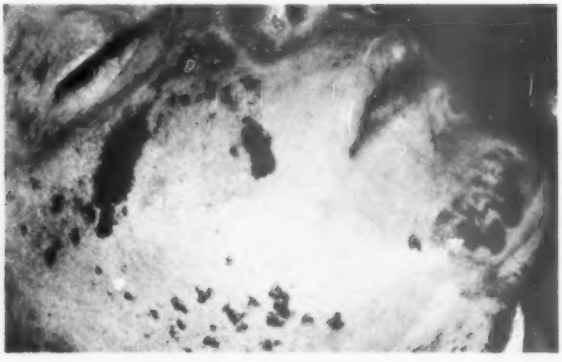
One of the many procedures where Adrenosem® SALICYLATE has been especially effective when used preoperatively

The photographs below are of two typical cases in 200 dermabrasion procedures[4] over a period of two years.

Case #1 Left cheek untreated



Case #1 Right cheek, after treatment with Adrenosem

Case #2 Left cheek untreated

Case #2 Right cheek, after treatment with Adrenosem

Write for literature describing the action and uses of Adrenosem Salicylate

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1. *Dripps, R.D.: Hazards of the Immediate Postoperative Period, J.A.M.A. 7:795 (Oct. 19, 1957) [This reference reviews postoperative hazards, and does not refer to Adrenosem Salicylate]*
2. *Ersner, M.S., and Lerner, S.S.: M. Clin. North America 40:1749 (Nov., 1956)*
3. *Peele, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat, N. Carolina M.J. 17:98 (March, 1956)*
4. *Brown, W.S.: The Use of Adrenosem Salicylate to Control Postoperative Bleeding in Plastic Surgery: Dermabrasion, Northwest Medicine. In Press.*
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6. *Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. 55:886 (Mar., 1956)*
7. *N.N.R., 1957, p. 265*

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Dosage: One tablespoonful at bedtime

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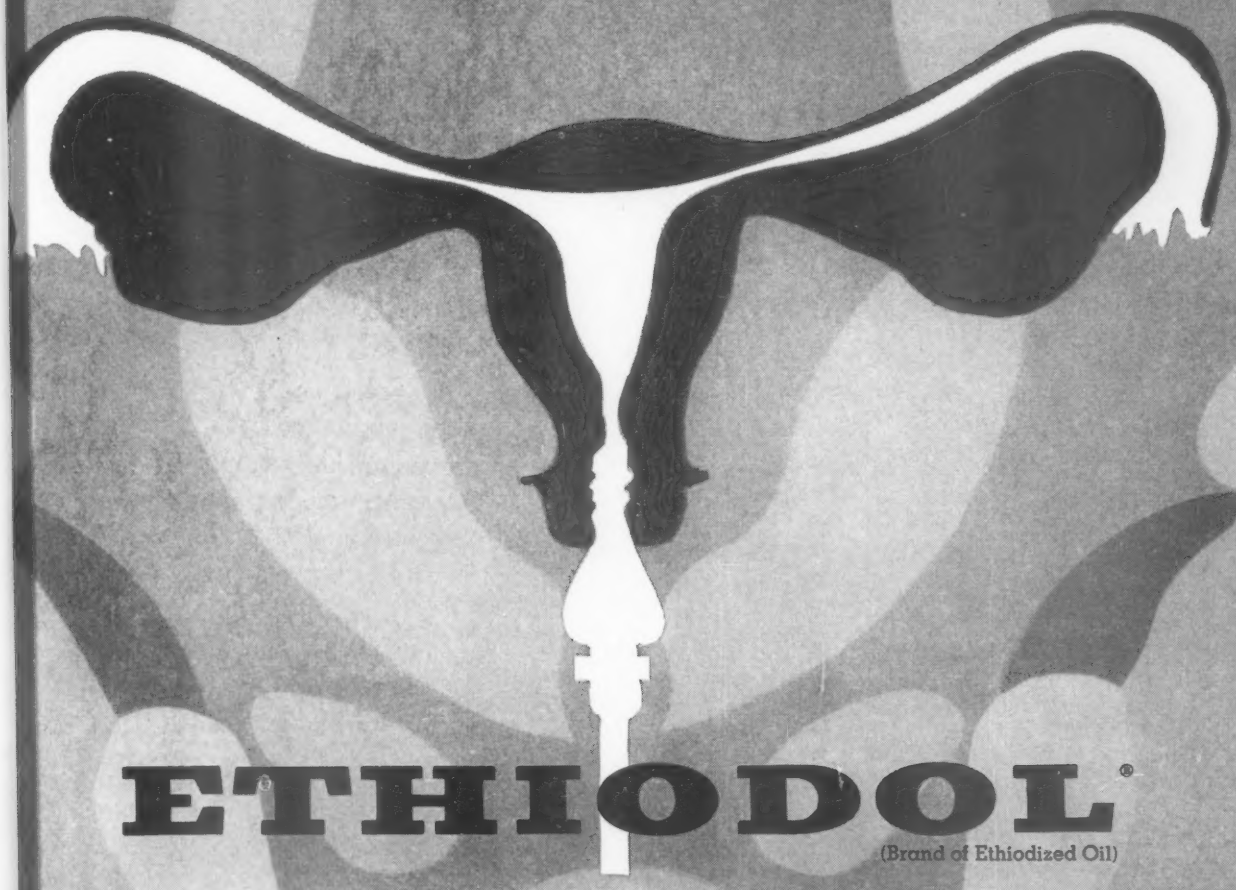

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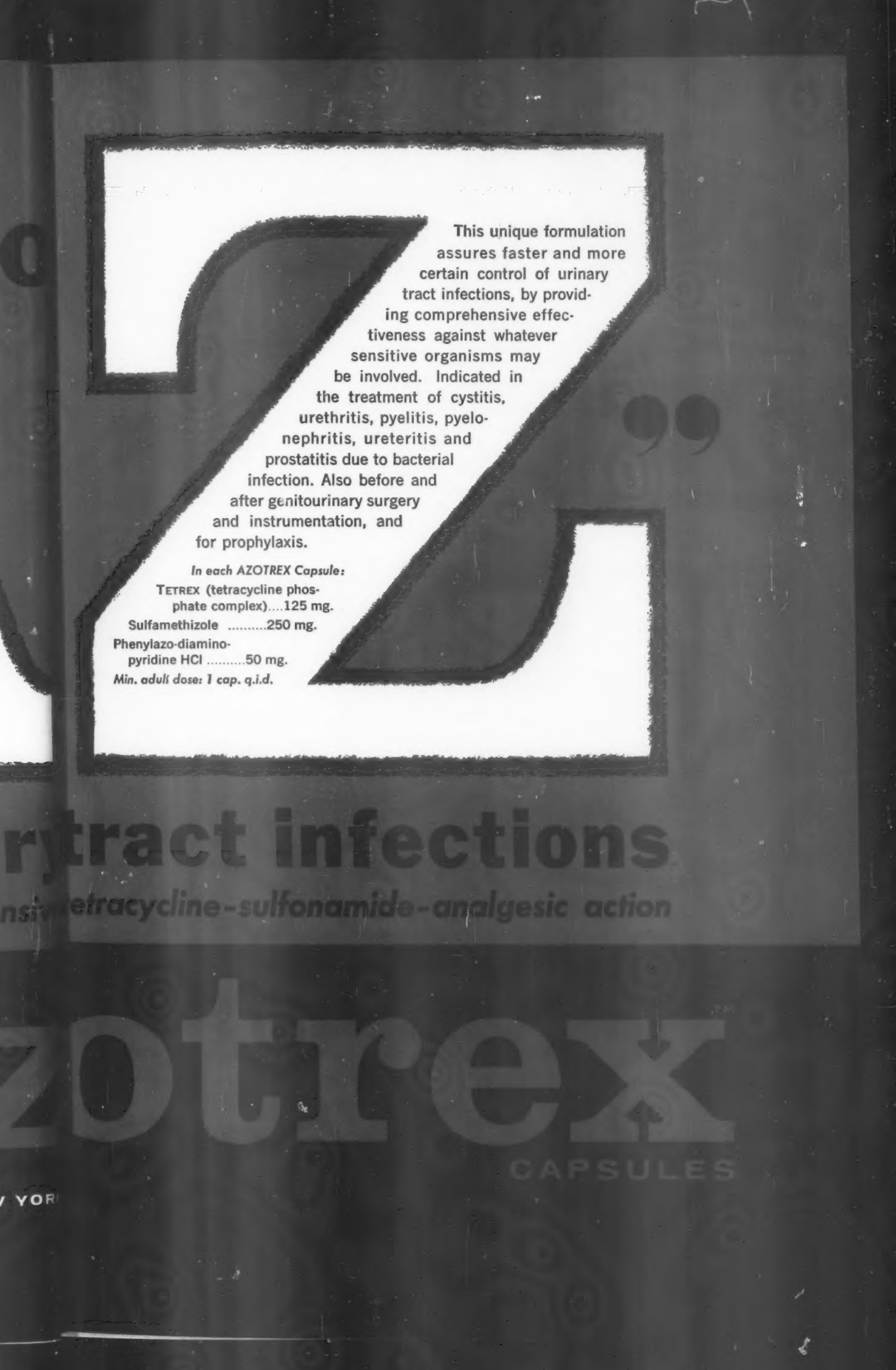
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In each AZOTREX Capsule:
TETREX (tetracycline phosphate complex)....125 mg.
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Min. adult dose: 1 cap. q.i.d.
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tetracycline-sulfonamide-analgesic action
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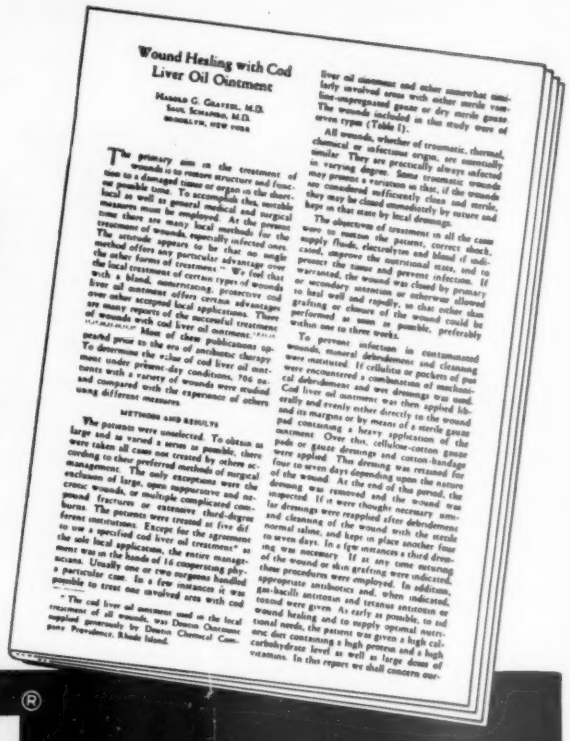
16 surgeons

participated in these

new extensive studies[1]

demonstrating that



Wound Healing with Cod Liver Oil Ointment

Harold G. Grayzel, M.D.
Saul Schapiro, M.D.
Brooklyn, New York

The primary aim in the treatment of wounds is to restore structure and function to a damaged tissue or organ in the shortest possible time. To accomplish this, suitable local as well as general medical and surgical measures must be employed. At the present time there are many local methods for the treatment of wounds, especially infected ones. The rationale appears to be that no single method offers any particular advantage over the other forms of treatment.* We feel that the local treatment of certain types of wounds with a bland, moisturizing, protective cod liver oil ointment offers certain advantages over other accepted local applications. There are many reports of the successful treatment of wounds with cod liver oil ointment.

Most of these publications appeared prior to the era of antibacterial therapy. To determine the value of cod liver oil ointment under present-day conditions, 706 patients with a variety of wounds were studied and compared with the experience of others using different measures.

METHODS AND RESULTS

The patients were unselected. To obtain as large and as varied a series as possible, there were taken all cases now treated by others according to their preferred methods of surgical management. The only exceptions were the exclusion of large, open, suppurative and necrotic wounds, or multiple complicated compound fractures or extensive third-degree burns. The patients were treated at five different institutions. Except for the agreement to use a specified cod liver oil treatment* as the sole local applications, the entire management was on the hands of 16 cooperating physicians. Usually one or two surgeons handled a particular case. In a few instances it was possible to treat one involved area with cod liver oil ointment and other somewhat similarly involved areas with other sterile vaseline-impregnated gauze or dry sterile gauze of one type (Table I).

All wounds, whether of traumatic, thermal, chemical or infectious origin, are essentially similar. They are practically always infected to varying degree. Some traumatic wounds may present a variation in that, if the wounds are considered sufficiently clean and sterile, they may be closed immediately by suture and kept in that state by local dressings.

The objectives of treatment in all the cases were to sustain the patient, correct shock, supply fluids, electrolytes and blood if indicated, improve the nutritional state, and to warranted, the wound was closed by primary or secondary suture or otherwise allowed to heal well and rapidly, so that other also performed as soon as possible, preferably within one to three weeks.

To prevent infection in contaminated wounds, mechanical debridement and cleansing were instituted. If cellulitis or pockets of pus were encountered a combination of mechanical debridement and wet dressings was used. Cod liver oil ointment was then applied liberally and evenly either directly to the wound and its margins or by means of a sterile gauze pad containing a heavy application of the ointment. Over this, cellulose-cotton gauze pads or gauze dressings and cotton-bandage were applied. This dressing was retained for four to seven days depending upon the nature of the wound. At the end of this period, the dressing was removed and the wound was inspected. If it were thought necessary ointment dressings were reapplied after debridement and cleansing of the wound with the sterile normal saline, and kept in place another four to seven days. In a few instances a third dressing was necessary. If at any time suturing of the wound or skin grafting were indicated, these procedures were employed. In addition, appropriate antibiotics and, when indicated, gas-bacilli antitoxin and tetanus antitoxin or toxoid were given. As early as possible, to aid wound healing and to supply optimal nutritional needs, the patient was given a high caloric diet containing a high protein and a high carbohydrate level as well as large doses of vitamins. In this report we shall concern our-

* The cod liver oil ointment used in the local treatment of all wounds, was Desitin Ointment supplied generously by Desitin Chemical Company, Providence, Rhode Island.

DESITIN® ointment

promotes "early, clean and healthy healing"

in

- traumatic and infectious wounds
- burns (first, second, third degree)
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This confirms previous findings regarding the efficacy of soothing, protective, non-irritant Desitin Ointment—rich in cod liver oil—to accelerate healing in many other skin conditions . . . diaper rash, ulcers (decubitus, varicose, diabetic), etc.

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1. Grayzel, H. G., and Schapiro, S.: Western J. Surgery, Obstet. & Gyn., Oct. 1956.

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NON-NARCOTIC

Potently Analgesic

Effectively Anti-inflammatory

2 ZACTIRIN tablets are equivalent in analgesic potency to ½ grain of codeine plus 10 grains of acetylsalicylic acid.

Supplied: Distinctive, 2-layer yellow-and-green tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

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extra protection for every conception

Decidual bleeding due to capillary fragility leads to abortion

Hesper-C Prenatal

with capillary-protective factors plus vitamins-minerals

a precaution in every pregnancy
a necessity in habitual abortion[1,2]

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HESPERIDIN COMPLEX	600 mg.	Thiamine Mononitrate	7.5 mg.
ASCORBIC ACID	600 mg.	Riboflavin	4.5 mg.
Ferrous Gluconate (15 mg. iron)	130 mg.	Nicotinamide	30.0 mg.
Calcium Pantothenate	6 mg.	Vitamin B_{12}	4.5 mcg.
Calcium Carbonate (500 mg. calcium)	1.25 Gm.	Folic Acid	0.3 mg.
Vitamin A Acetate	6,000 U.S.P. Units	Pyridoxine Hydrochloride	10.0 mg.
Vitamin D_2	1,200 U.S.P. Units	Copper Sulfate (3.0 mg. copper)	12.0 mg.
		Potassium Iodide (0.3 mg. iodine)	0.4 mg.

Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

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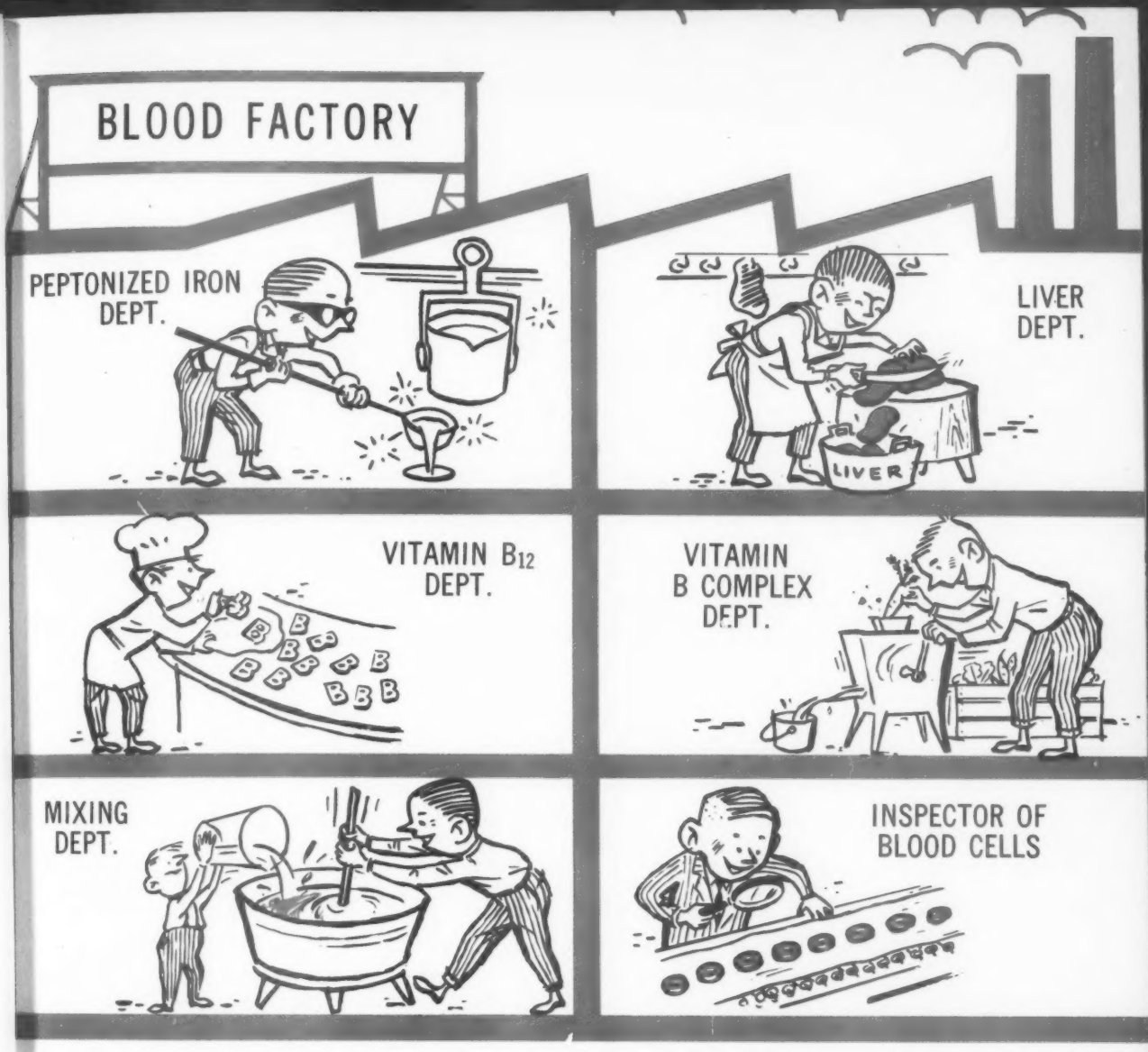
2. Dill, L. V.: M. Ann. District of Columbia 23:667, 1954.

THE NATIONAL DRUG COMPANY

Philadelphia 44, Pa.

Products of Original Research

HCP 1800/57



The preferred hematinic with **PEPTONIZED** *iron*

LIVITAMIN®

Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

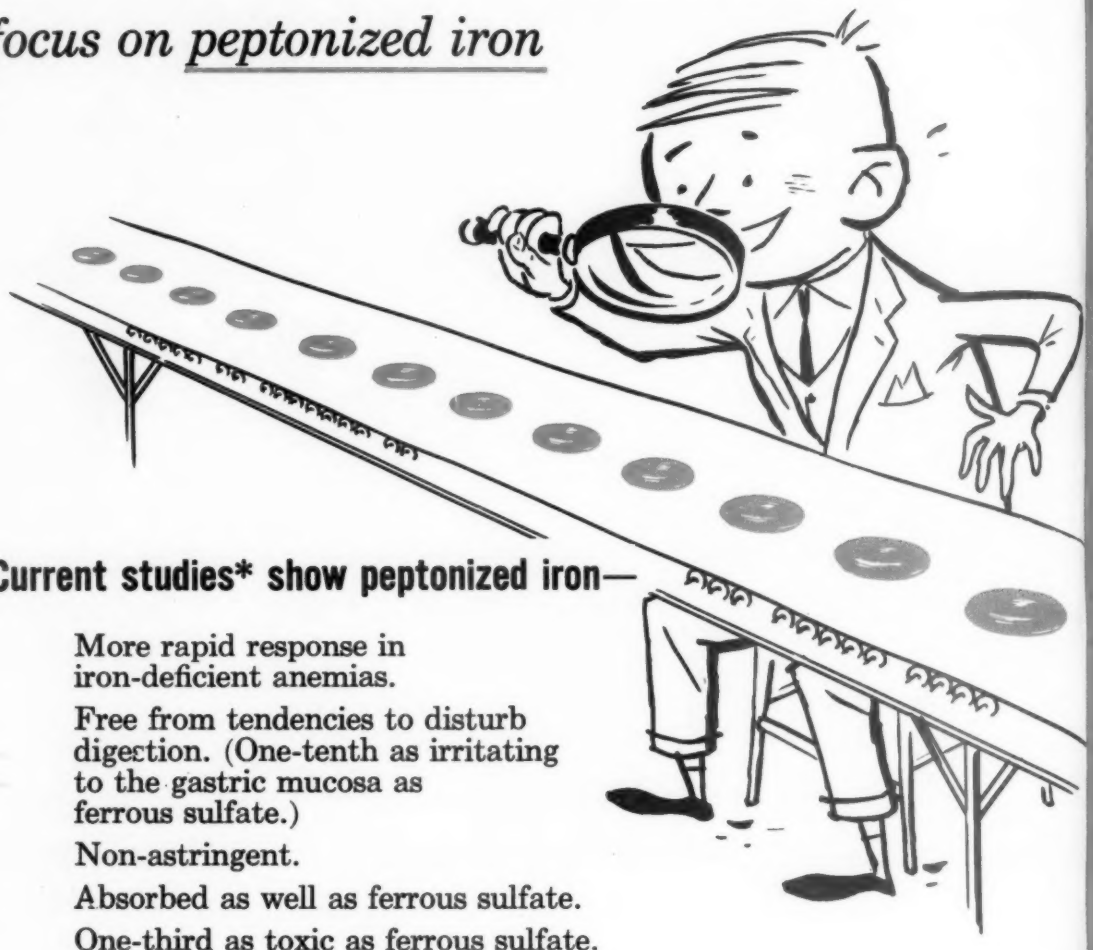
Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} Activity (derived from Cobalamin conc.)	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

The S. E. MASSENGILL Company BRISTOL, TENNESSEE
NEW YORK • KANSAS CITY • SAN FRANCISCO

For predictable therapeutic advantages . . .

focus on peptonized iron



Current studies* show peptonized iron—

More rapid response in iron-deficient anemias.

Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)

Non-astringent.

Absorbed as well as ferrous sulfate.

One-third as toxic as ferrous sulfate.

LIVITAMIN® with Peptonized I

*Currently, mailings will
forwarded only at your requ
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ture.*

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition *1*:35 (Jan.-Feb., 1957).

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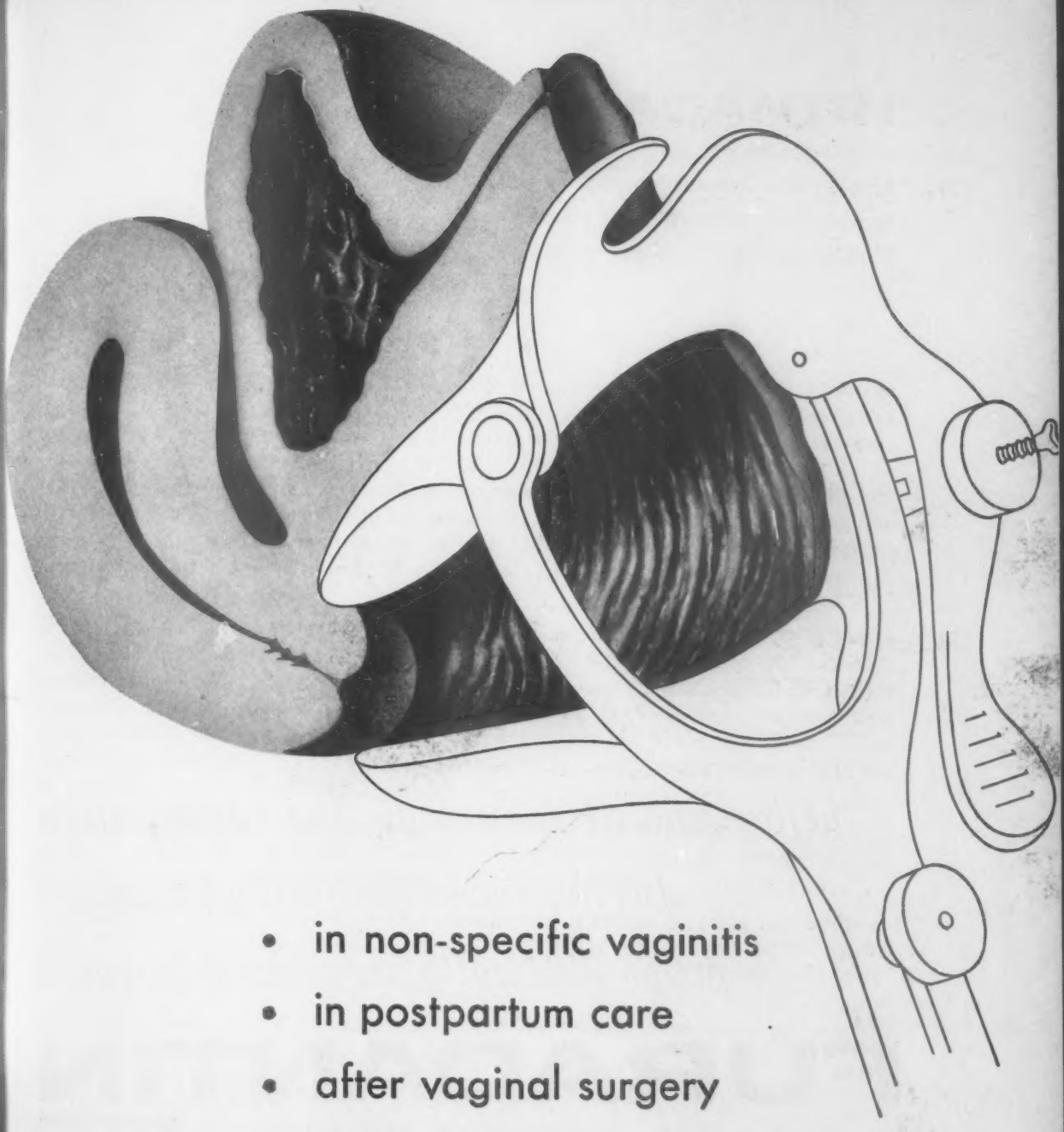


- in non-specific vaginitis
- in postpartum care
- after vaginal surgery

Triple Sulfa Cream

TRADEMARK

Ortho

CATHETERS,
SOUNDS AND
CYSTOSCOPES:
SOURCES OF
INFECTION

before and after urologic instrumentation

during indwelling catheterization

prophylactically in urologic surgery

FURADANTIN®

brand of nitrofurantoin

"The catheter **is probably the most common agent responsible for resistant urinary tract infections. . . . A catheter seeds the bladder with urethral bacteria."[1]**

During indwelling catheterization, **"the urethra is distended by a foreign body for days or weeks. The response to this is production of a sheath of mucopurulent exudate around the catheter, providing a splendid medium for growth of microorganisms. Infection of the bladder cavity is almost inevitable under these circumstances. . . ."[2]**

"One further danger of urethral instrumentation **is that it may produce a transient bacteremia. . . . In view of the possibility that infection of the kidneys may take place via the blood stream, *the bacteremia of urethral instrumentation probably represents one of the ways in which infection is transferred from lower to upper urinary tract.*** **. . . Bacteremia has been found in a significant proportion of cases immediately after the passage of a sound or cystoscope."[2]**

FURADANTIN

". . . may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants."[3]

■ **RAPID ACTION.** FURADANTIN, a specific for urinary tract infections, provides rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria and organisms resistant to other agents including Proteus and certain strains of Pseudomonas. "Nitrofurantoin (FURADANTIN) has been found to be highly effective in the treatment of chronic urinary tract infection following prostatectomy. Treatment resulted in an abrupt fall in the number of bacteria in the urine, and, in almost one half of the patients, sterile urines were obtained during treatment. The drug was most effective against infections with E. coli and B. proteus."[4]

■ **EXCELLENT TOLERANCE.** There have been no reports of injury to kidneys, liver or blood-forming organs as a result of FURADANTIN therapy. No cases of monilial superinfection, crystalluria or staphylococcic enteritis have ever been reported. In one study, a particularly encouraging finding "was the fact that nitrofurantoin (FURADANTIN) did not cause diarrhea in any of the patients. . . . This might be a consideration in the choice of an antimicrobial drug, particularly if the patient is in the hospital."[3]

■ **NEGLIGIBLE DEVELOPMENT OF BACTERIAL RESISTANCE.** In six years of extensive use in the treatment of genitourinary tract infections, development of bacterial resistance remains negligible with FURADANTIN.

AVERAGE FURADANTIN DOSAGE: In acute, complicated or refractory cases and in chronic infections of adults: 100 mg. q.i.d. In acute, uncomplicated urinary tract infections, for prophylaxis and postoperatively in urologic surgery: 50 mg. q.i.d. (If patient is unresponsive after 2 or 3 days, increase dose to 100 mg. q.i.d.)

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100. Oral Suspension, 25 mg. per 5 cc. tsp., 60 cc. bottle.

NOW for hospitalized patients, for severe urinary tract infections when peroral administration of Furadantin is not feasible and for serious infections as septicemia (bacteremia) when the bacterium is sensitive.
NEW, LIFESAVING **FURADANTIN** *Intravenous Solution*

FURADANTIN Sensi-Discs for bacterial sensitivity tests are available from Baltimore Biological Laboratories.

REFERENCES: 1. Lich, R., Jr.: J. Arkansas M. Soc. 52:271, 1956. 2. Beeson, P. B.: Yale J. Biol. 28:81, 1955. 3. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 4. Draper, J. W., et al.: J. Urol. 72:1211, 1954.

NITROFURANS *a new class of antimicrobials . . . neither antibiotics nor sulfonamides*

EATON LABORATORIES, NORWICH, NEW YORK

A brighter "Good morning, doctor!"

No complaints about

* post-episiotomy,
* tender hemorrhoids,
* or fissured nipples when you prescribe

Americaine® Topical Anesthetic

Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

What about sensitivities? None reported in over 11,800 published clinical cases[1]...negligible incidence in 10 years' steadily growing use.

Americaine Aerosol

For quick spray application. Available in 3 oz. prescription size, also 5.5 oz. and 11 oz. dispensers.

Americaine Ointment

For simple manual application. Available in 1 oz. tube w/applicator

1. References on request.

ARNAR-STONE LABORATORIES, INC., *Mount Prospect, Ill.*

AN IMPORTANT ADVANCE IN MENOPAUSAL THERAPY

Because it replaces *half* control with *full* control.
Because it treats the *whole* menopausal syndrome.
Because *one* prescription manages *both* the psychic and somatic symptoms.

SUPPLIED: Bottles of 60 tablets.
Each tablet contains:

MILTOWN® (meprobamate, Wallace) ..... **400 mg.**
2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate.
U. S. Patent No. 2,724,720.

Conjugated Estrogens (equine) ..... **0.4 mg.**
Licensed under U. S. Patent No. 2,429,398.

DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Samples and literature on request.

Two-dimensional treatment of the menopause

"Milprem"

MILTOWN® A Proven Tranquilizer + CONJUGATED ESTROGENS (EQUINE) A Proven Estrogen

WALLACE LABORATORIES, *New Brunswick, N. J.*
who discovered and introduced Miltown, the original meprobamate.

Psychic cycle

Anxiety, tension, and related symptoms exist in most gynecologic disturbances.

Symptoms of premenstrual tension (irritability, nervousness, headaches) were completely relieved with 'Miltown' in 78% of patients, and substantially relieved in all others studied.[1]

Patients with tension symptoms during menstruation became symptom-free on 'Miltown' therapy.[2]

'Miltown' *relaxes both mind and skeletal muscle* and alleviates somatic symptoms of anxiety, tension, and fear (usual dosage: 400 mg. q.i.d.). 'Miltown' therapy is notably safe, even in pregnancy,[3] and does not impair mental or physical efficiency.

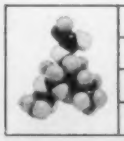
References:

1. *Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. J.A.M.A.* **164**:*638, June 8, 1957.*

2. *Selling, L. S.: Clinical study of a new tranquilizing drug: use of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate). J.A.M.A.* **157**:*1594, April 30, 1955.*

3. *Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec.* **9**:*703, June 1957.*

Miltown®



THE ORIGINAL MEPROBAMATE
DISCOVERED & INTRODUCED BY
WALLACE LABORATORIES
NEW BRUNSWICK, NEW JERSEY

CM-5793

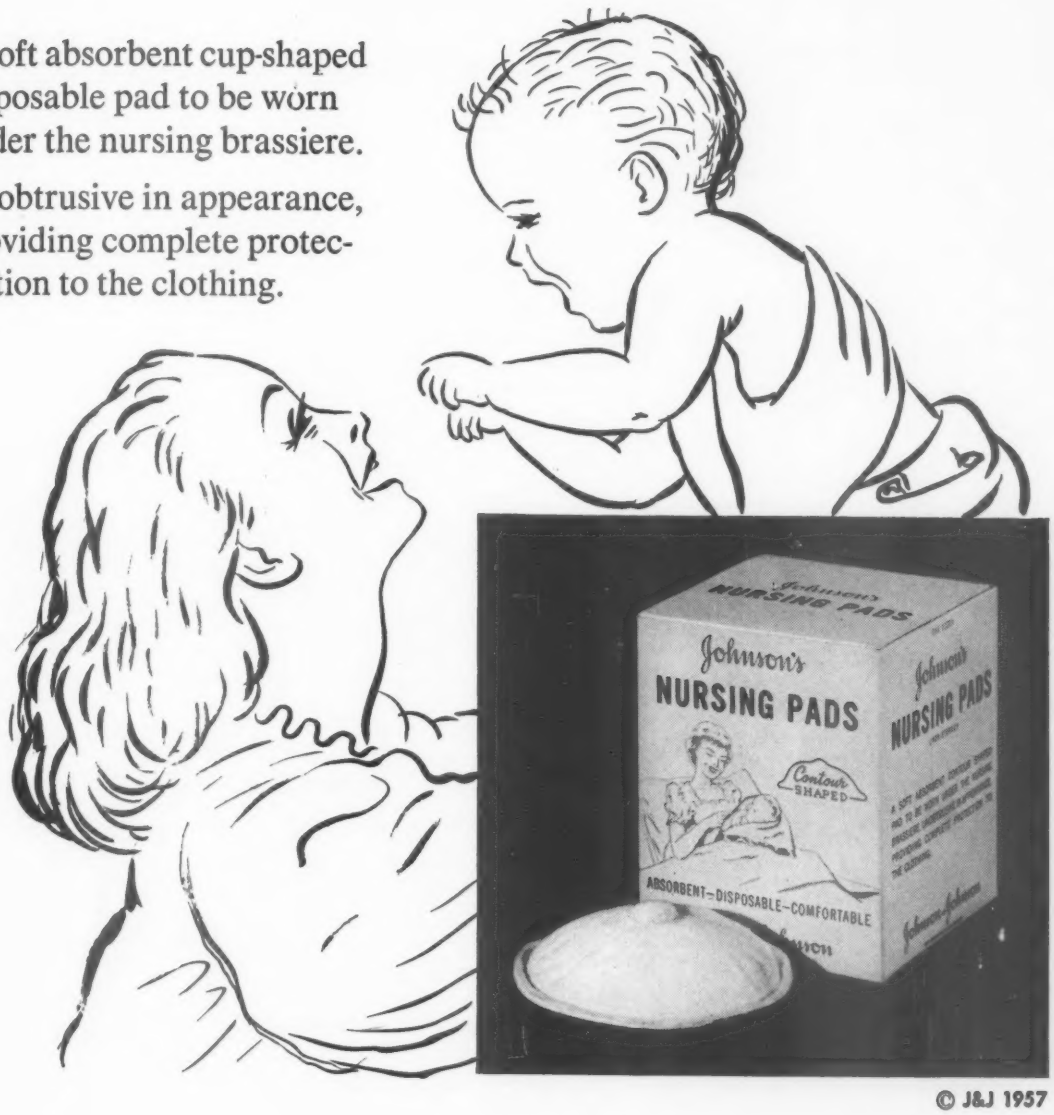
NEW.

Johnson's
contour-shaped
disposable

NURSING PADS

A soft absorbent cup-shaped disposable pad to be worn under the nursing brassiere.

Unobtrusive in appearance, providing complete protec-tection to the clothing.



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ANOTHER QUALITY PRODUCT FROM THE RESEARCH LABORATORIES OF

Johnson & Johnson

In urinary-tract infections

HIGH TISSUE LEVELS

HIGH BLOOD LEVELS

LOW TOXICITY

SUSPENSION **TABLETS**

SULFOSE®

Triple Sulfonamides, Wyeth
(Trisulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine)

PHYSICIANS' COUNCIL · INFORMATION ON CHILD HEALTH ·

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

Wyeth®
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the critical
fibrinogen
index in
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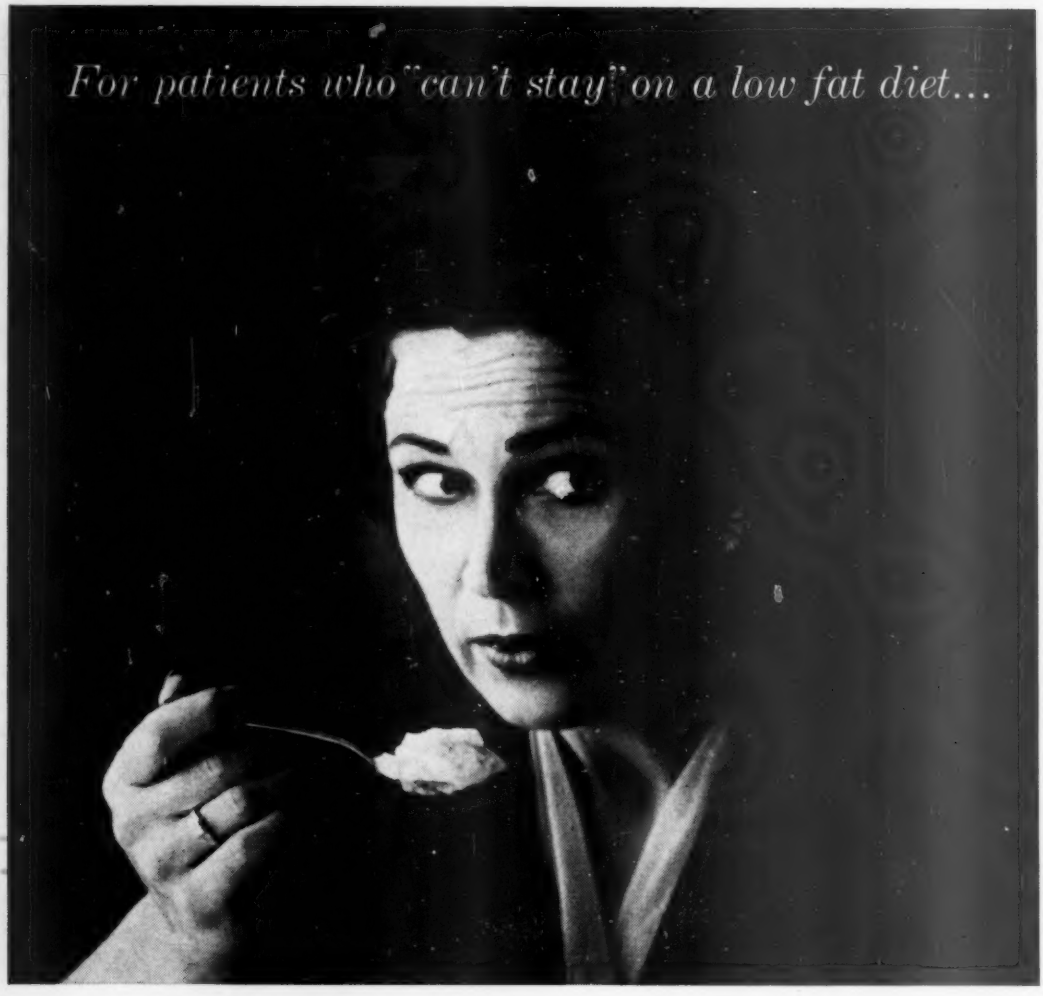


New Carnation Instant "self-enriched"

25% MORE PROTEIN, RICHER FLAVOR THAN ORDINARY NONFAT MILK!

Carnation Instant is a new crystal form of nonfat milk—and the *first* to bring Self-Enriched flavor and Self-Enriched nutritional advantages to low fat diets. Delicious for drinking, Carnation Instant enriches itself merely by the addition of one extra tablespoon of crystals per glass or ⅓ cup extra crystals per quart.

Result: "Difficult" patients stay on low fat diets. They respond to a richer and more palatable flavor, receive 25% more protein with each glassful – actually 41.3 grams of essential protein per quart.

CONVENIENT. And Carnation Instant is convenient, too– mixes instantly and completely even in ice-cold water–with a slight twirl. Ready to drink, immediately, *in the office,* at home or away from home. It's always cupboard-handy.

But surely...

the lady will be dainty

- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder is buffered to *maintain* an acid condition in the vaginal mucosa. It is more effective than vinegar and simple acid douches.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill® powder

when recommending a vaginal douche

INDICATIONS:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

Currently, mailings will be forwarded only at your request.
Write for samples and literature.

The S. E. MASSENGILL Company BRISTOL, TENNESSEE
NEW YORK SAN FRANCISCO KANSAS CITY

In modern feminine hygiene

and therapy

massengill® powder

Massengill Powder has cosmetic elegance. Its clean, refreshing fragrance is acceptable to t most fastidious for therapeutic or routine hygienic use. Massengill Powder solutions a easily prepared, convenient to use, nonstaining. They effectively cleanse, deodorize a soothe the vaginal mucosa, while their mild astringent properties tend to decrease vagin secretions.

CLEAN-UP AFTER ANTIBIOTICS

Following intensive antibiotic therapy, increasing numbers of female patients return complaining of vulvar pruritus or vaginitis . . . and profuse vaginal discharge.

Most of these present the classical picture of Monilia albicans, Trichomonas vaginalis or mixed infections. When these infections occur, regular use of Massengill Powder, with its pH of 3.5 to 4.5, helps restore the normal acidity of the vaginal tract. At this normal pH the growth of pathogenic organisms is inhibited and the growth of the normal vaginal flora encouraged,[1] thus reducing the barriers to specific medication.

LOW pH RETENTION

Massengill Powder is buffered to retain an acid condition. In a recent clinical observation, ambulatory patients—with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for a period of 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours. Simple acid douches (vinegar or lactic acid) are quickly neutralized by an alkaline vaginal mucosa; therefore, they are somewhat unsatisfactory in maintaining the required acid pH of the vagina.[2]

LOWER SURFACE TENSION

Massengill Powder in the standard solution h a surface tension of 50 dynes/cm. as compar to that of water and simple acid solutions wi 72 dynes/cm. This added property of reduc surface tension enables Massengill Powder penetrate into and cleanse the folds of t vaginal mucosa, thus increasing the therapeu effectiveness. Lowered surface tension mak the cell wall and cytoplasmic membrane of t infecting organism more permeable and th more susceptible to specific therapy.[2]

SUPPLY

Massengill Powder is supplied in glass jars the following sizes:

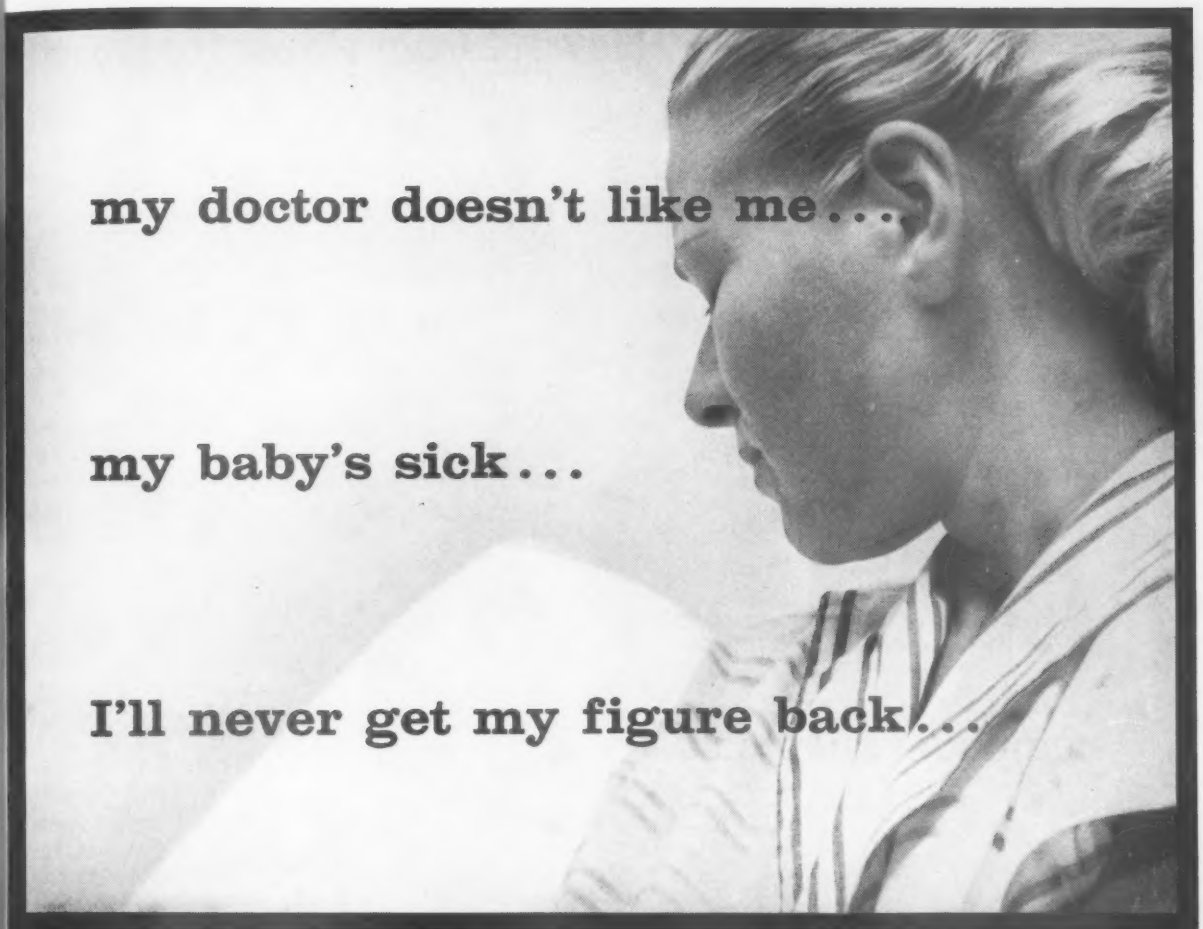
Small, 3 oz.
Medium, 6 oz.
Large, 16 oz.
Hospital Size, 5 lbs.

Pads of douching instructions for patient u available on request.

REFERENCES

1. Lang, W.R., Rakoff, A.E., Am. Geriatrics S *1*:520 (1953).
2. Arnot, P.H., The Problem of Douching, West Journal of Surg., Obs., and Gyn., Vol. 62, No. 2 (1954).

The S. E. MASSENGILL Company BRISTOL, TENNESSEE
NEW YORK SAN FRANCISCO KANSA



Excessive anxiety and tension after childbirth are often the result of the patient's inability to cope with the immensity of her experience.

'Thorazine' is useful in relieving the severe anxiety and apprehension that exceed the ordinary discomfort and emotional stress experienced by all.

THORAZINE*

chlorpromazine, S.K.F.

one of the fundamental drugs in medicine

Available: tablets, Spansule* sustained release capsules, ampuls, multiple dose vials, syrup and suppositories.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

New... from Pfizer Research

84

compounds tested

1

compound unexcelled

Progress has been made in antibiotic therapy through the use of absorption-enhancing agents, resulting in higher, more effective antibiotic blood levels.

For the past two years, in a continuing search for more effective agents for enhancing oral antibiotic blood levels, our Research Laboratories screened eighty-four adjuvants, including sorbitol, citric acid, sodium hexametaphosphate, and other organic acids and chelating agents as well as phosphate complex and other analogs. After months of intensive comparative testing, glucosamine proved to be the absorption-enhancing agent of choice. Here's why:

1 Crossover tests show that average blood levels achieved with glucosamine were markedly higher than those of other enhancing agents screened. In some cases this effect was more than double.

2 Of great importance to the practicing physician is the consistency of the blood level enhancement achieved with glucosamine. Extensive tests show that the enhancing effect with glucosamine occurs in a greater percentage of cases than with any other agent screened.

3 Glucosamine is a nontoxic physiologic metabolite occurring naturally and widely in human secretions, tissues and organs. It is nonirritating to the stomach, does not increase gastric secretion, is sodium free and releases only four calories of energy per gram. Also, there is evidence that glucosamine may favorably influence the bacterial flora of the intestinal tract.

For these reasons glucosamine provides you with an important new adjuvant for better enhancement of antibiotic blood levels. Tetracycline, potentiated physiologically with glucosamine, is now available to you as COSA-TETRACYN.

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

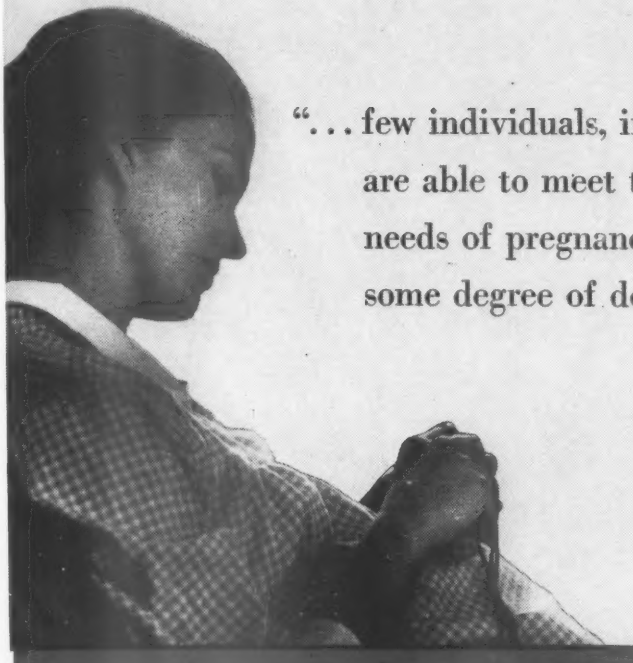
Capsules 250 mg. and 125 mg.

The most widely used broad-spectrum antibiotic now potentiated with glucosamine, the enhancing agent of choice

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

*Trademark



"... few individuals, if any, are able to meet the increased needs of pregnancy without suffering some degree of deprivation."[1]

Help assure your patients nutritionally perfect pregnancies

prescribe

Engran

Squibb Vitamin-Mineral Supplement

just 1 small capsule-shaped tablet daily

Each small capsule-shaped tablet provides:

Vitamin A	5,000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Vitamin K (as menadione)	0.5 mg.
Thiamine Mononitrate	3 mg.
Riboflavin	3 mg.
Pyridoxine HCl	2 mg.
Vitamin B_{12} Activity Concentrate	2 mcg.
Folic Acid	0.25 mg.
Niacinamide	20 mg.
Calcium Pantothenate	5 mg.
Ascorbic Acid	75 mg.
Calcium, elemental (as calcium carbonate, 375 mg.)	150 mg.
Iron, elemental (as ferrous sulfate exsiccated, 33.6 mg.)	10 mg.
Iodine, elemental (as potassium iodide, 0.2 mg.)	0.15 mg.
Potassium (as the sulfate)	5 mg.
Copper (as the sulfate)	1 mg.
Magnesium (as the oxide)	6 mg.
Manganese (as the sulfate)	1 mg.
Zinc (as the sulfate)	1.5 mg.

Supply

Bottles of 100 and 1000. For your patient's convenience, *Engran Term-Pak* provides 250 tablets – enough to last until term—in a handsome reusable glass jar plus a purse-size dispenser.

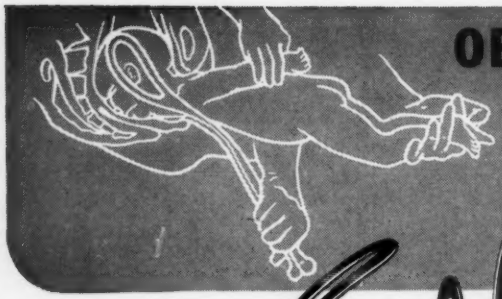
Reference: 1. Tompkins, W. T. in Wohl, M. G. and Goodhart, R. S.: *Modern Nutrition in Health and Disease*, Lea & Febiger, Philadelphia, 1955, p. 886.

Advantages

- specifically formulated for the mother-to-be
- generous amounts of 11 vitamins and 8 minerals
- contains vitamins A, C, D, K and the B complex
- provides phosphorus-free calcium, plus iron and trace elements

SQUIBB

Squibb Quality—the Priceless Ingredient



OBSTETRICAL FORCEPS *by Sklar*

STAINLESS STEEL . . . AMERICAN MADE

Made to exacting standards of fine workmanship and materials, Sklar obstetrical forceps are outstanding for their dependability, design and precision construction.

No. 410-60. Hirst, length 10 inches.

No. 410-110. Piper, for after coming head in Breech presentation, length 17½ inches.

No. 410-10. DeLee, standard, length 14 inches.

No. 410-125. Hawks-Dennen, with traction curve, length 15½ inches.

No. 410-65. Barton, length 14 inches.

No. 410-70. Barton Traction Handle, (not illustrated).

No. 410-75. Kieland, length 15½ inches.

No. 410-80. Luikart, length 15½ inches.

No. 410-90. McLean, blades modified by Luikart, length 14 inches.

No. 410-30. Bill traction handle (not illustrated) may be used with any obstetrical forceps with standard type handle.

SKLAR products available through accredited Surgical Supply Distributors.

Sklar LONG ISLAND CITY, N. Y.

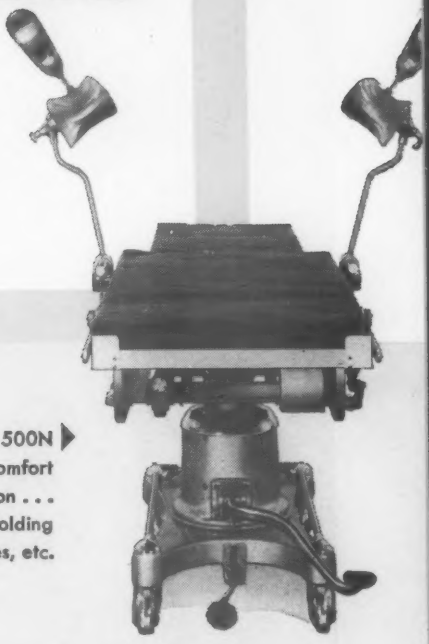
CAUTION! If the name SKLAR is not stamped on the instrument, it is not a genuine Sklar Product.

American-MacEachern

22" Obstetrical Table

for Abdominal or

Perineal Route Delivery



The "clean" lines of the 500N table provide maximum comfort and freedom for the surgeon . . . with toe space, folding handles, etc.

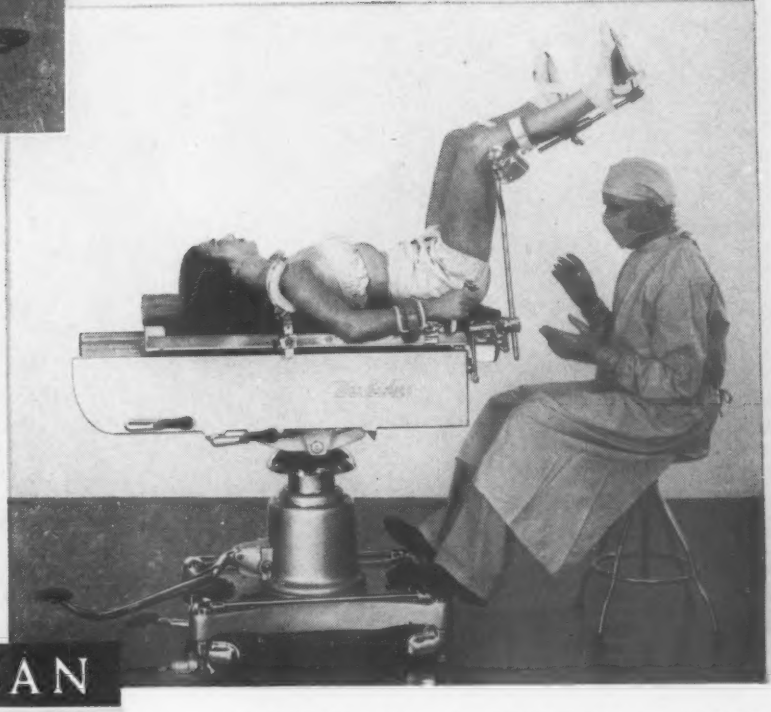
● The new 22" 500N table assures both the patient and the obstetrician the fullest advantages of modern obstetrical practice under *all* conditions.

The growing practice of performing Cesarian sections in the O. B. room . . . without moving or disturbing the patient . . . is made easy by the 22" surgery width of the 500N. Yet the table will accommodate even the largest patient during normal delivery and the universally adjustable knee and foot rests accommodate all patients from the tallest to the shortest.

Write for bulletin TC-224.

If non-elective Cesarian section is indicated, patient is quickly and easily positioned for surgery simply by lowering extremities and raising the foot section. The anesthetist need not change position of head of patient.

15" height adjustment and every known obstetrical posture from high lithotomy to Walcher position provides convenient approach to the perineal field.



AMERICAN STERILIZER

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OFFICES IN 14 PRINCIPAL CITIES

key
to
safety
in
surface
anesthesia

Tronothane®
(PRAMOXINE, ABBOTT)

Not a "caine" derivative. In over 15,600 case studies, sensitization was negligible, with no signs of toxicity or cross-sensitization.

Abbott

superior vulvovaginal therapy

with

trichotine®

a surface-active detergent
which dissolves the viscid film

a bactericide and fungicide
which penetrates and destroys the microorganisms

an antipruritic
for prompt relief from itching and discomfort

a psychic and aesthetic adjunct
providing an immediate sense of well-being

indications:

Vaginitis and Vulvovaginitis – nonspecific, trichomonal, monilial, senile, diabetic, postoperative

Cervicitis – subacute and chronic

Pruritus Vulvae – hot pack applications

Office Clean-up – concentrated solutions

Hygienic Irrigations – postcoital, postmenstrual

suggestion:

Upon retiring, a TRICHOTINE douche followed by a VACID suppository provides maximum effectiveness and 24-hour pH control.

The TRICHOTINE formula contains sodium lauryl sulfate, sodium perborate, sodium borate, thymol, menthol, eucalyptol and methyl salicylate.

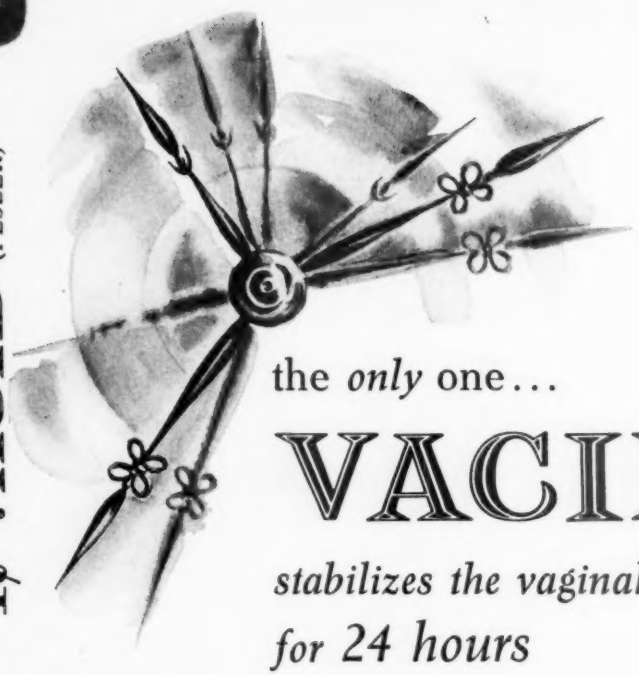
samples and literature upon request.

The Fesler Co., Inc.

375 Fairfield Ave. Stamford, Conn.

℞ **trichotine** (FESLER)

℞ VACID (FESLER)



the *only* one...

VACID®

stabilizes the vaginal pH for 24 hours

Extensive clinical experience demonstrates the therapeutic value of the continual maintenance of the normal physiologic pH in the treatment of trichomonal, monilial, and non-specific bacterial infections and in cervicitis.

Only Vacid provides a high capacity cationic exchange resin accurately buffered to stabilize the vaginal pH range at 4.0-4.5 for twenty-four hours.

Indications: **IN VAGINITIS** – trichomonal, monilial, non-specific

CERVICITIS – subacute and chronic, including eversions

POSTCAUTERY and **POSTCONIZATION**

PREGNANCY and **POSTPARTUM** – prophylactically and in infections.

Suggestion: Upon retiring, a Vacid suppository preceded by a Trichotine douche provides maximum effectiveness and 24-hour pH control.

FORMULA – Each Vacid suppository contains a high capacity polyacrylic cationic exchange resin (activated and buffered) combined with lactose.

samples and literature upon request

The Fesler Co., Inc.

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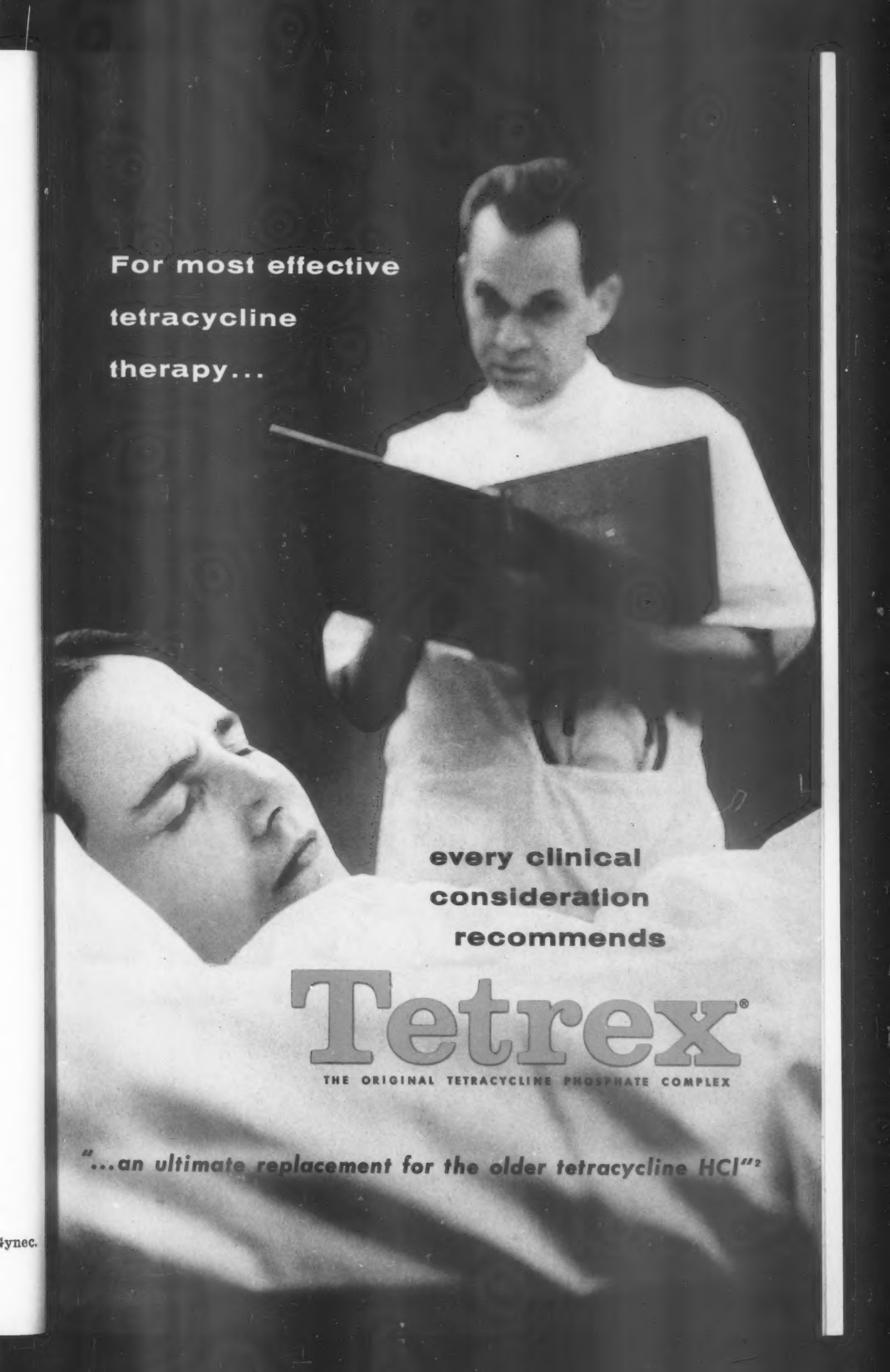
For most effective
tetracycline
therapy...
every clinical
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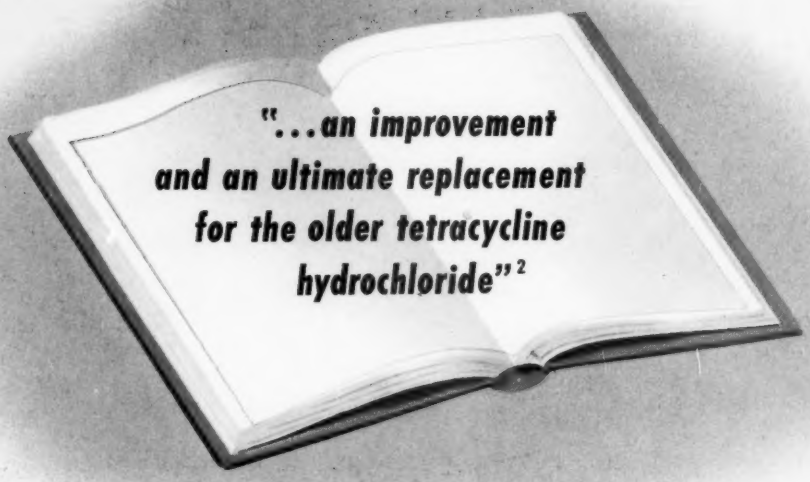
recommends
Tetrex®
THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX
"...an ultimate replacement for the older tetracycline HCl"[2]



Tetrex®

U.S. PAT. NO. 2,791,609

THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX

- *Significant tetracycline serum levels for 24 hours on a single intramuscular dose*[3,6]
- *Faster, higher, more prolonged tetracycline serum levels for earlier and more certain control of infection*[1,2,5,7-13]
- *A single, pure antibiotic (not a mixture)*
- *Clinically "sodium-free"*[2,7]
- *Equally effective orally, b.i.d. or q.i.d.*[2,7,9]
- *A convenient dosage form for every member of the family*

Bristol

A suitable TE
dosage form for
member of the f

TETREX Capsu
Tetracycline phos
complex—each c
equivalent to 2
tetracycline HCl

TETREX
Pediatric Caps
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Tetracycline phos
complex—each vial
alent to 250 mg.
cline HCl activity.

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complex—each vial
alent to 100 mg.
cline HCl activity.
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Tetracycline (pho
buffered) Syrup
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125 mg. tetracycli
activity.

TETREX
Pediatric Dro
Tetracycline (pho
buffered) Syrup
cc. equivalent to 1
tetracycline HCl

TETREX-APC
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Tetracycline phos
complex — each
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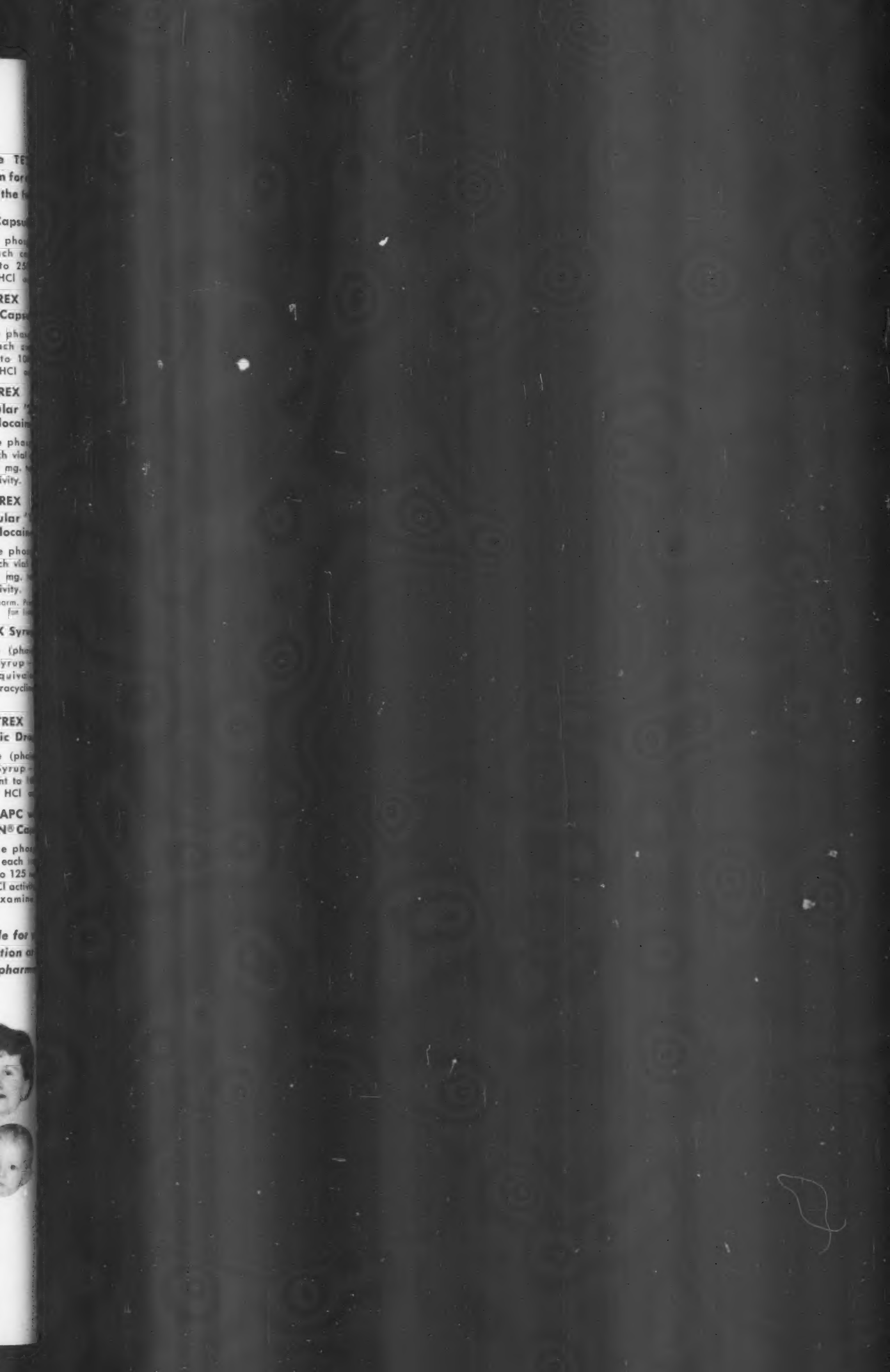
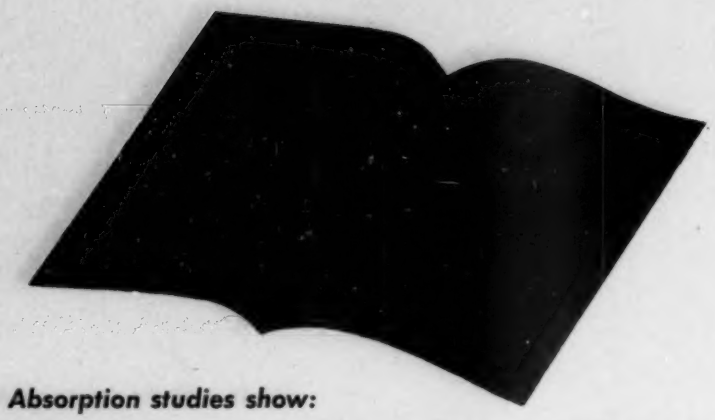


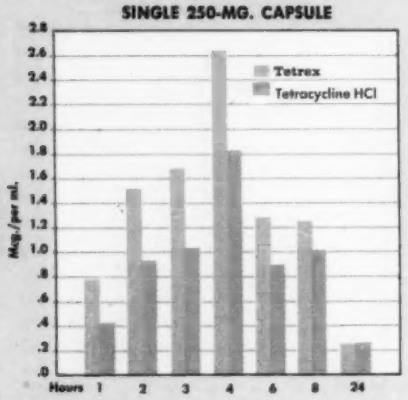


Absorption studies show:

Faster, higher, more prolonged tetracycline serum levels

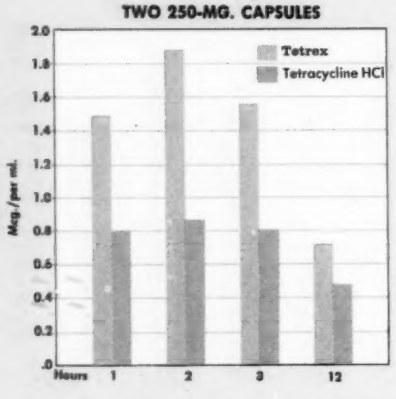
After oral administration—

SINGLE 250-MG. CAPSULE



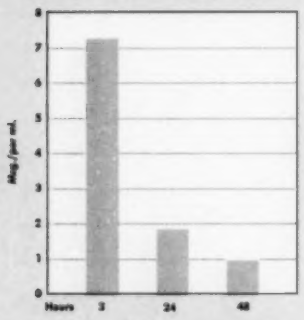
A composite of three separate absorption studies: serum levels "substantially higher"[2] or "markedly higher"[13] than with tetracycline HCl, and absorption "about twice as efficient."[5]

TWO 250-MG. CAPSULES



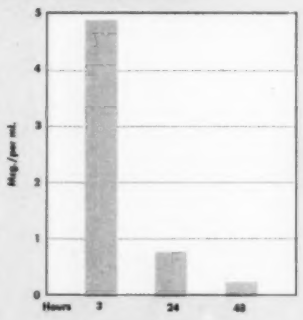
Average serum levels after administration of a single 500-mg. dose: "approximately twice as great" as those of a group receiving an equivalent dose of tetracycline HCl.[11]

After intramuscular administration—



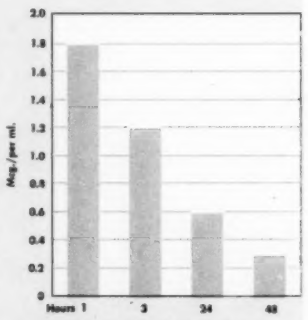
IN NEWBORN INFANTS

Median tetracycline serum levels following intramuscular injection of TETREX in newborn infants.[6] Dose: 25 mg./Kg. "Therapeutic" levels for at least 24 hours.



IN YOUNG CHILDREN

Median tetracycline serum levels following intramuscular injection of TETREX in young children.[6] Dose: 15 to 25 mg./Kg. "Surprisingly high" levels at 3 and 24 hours.



IN GERIATRIC PATIENTS

Average serum levels following intramuscular injection of a single 250-mg. dose in geriatric patients.[3] "Adequate" amounts of tetracycline activity present after 24 hours.

Rx

"...an improvement and an ultimate replacement for the older tetracycline hydrochloride"[2]

Tetrex®

THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX

Clinically proven—It has been determined that "blood concentrations correlate well with clinical response."[4] In clinical studies, the assurance that TETREX "would be more effective [than tetracycline HCl] in treating infections due to susceptible organisms"[11] has been fully confirmed.

Typically, when TETREX was administered to 686 patients in two studies, "all patients infected with tetracycline-sensitive organisms responded satisfactorily to therapy."[1,2]

A "remarkably low incidence of side reactions"[1] has been reported. In four studies involving 480 patients, for instance, side effects were so negligible as to require withdrawal of therapy in only 2 cases.[1,7,9,10]

BRISTOL LABORATORIES INC., SYRACUSE, NEW YORK

References:

1. Cronk, G. A., and Naumann, D. E.: Ant. Med. & Clin. Ther. 4:166, 1957. 2. Cronk, G. A., Naumann, D. E., and Casson, K.: Fifth Annual Symposium on Antibiotics, Washington, D.C., Oct. 2-4, 1957. 3. Dube, A. H.: *Ibid.* 4. Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Davis, Philadelphia, 1955, p. 55. 5. Kaplan, M. A., Dickison, H. L., Hubel, K. A., and Buckwalter, F. H.: Ant. Med. & Clin. Ther. 4:99, 1957. 6. Portney, B., Draper, T., and Wehrle, P. F.: Fifth Annual Symposium on Antibiotics, Washington, D.C., Oct. 2-4, 1957. 7. Prigot, A., Shidlovsky, B. A., and Felix, A. J.: Ant. Med. & Clin. Ther. 4:487, 1957. 8. Pulaski, E. J., and Isokane, R. K.: Ant. Med. & Clin. Ther. 4:408, 1957. 9. Putnam, L. E.: Ant. Med. & Clin. Ther. 4:470, 1957. 10. Rein, C. R., and Fleischmajer, R.: Ant. Med. & Clin. Ther. 4:422, 1957. 11. Shidlovsky, B. A., Prigot, A., Maynard, A. de L., Felix, A. J., and Hjelt-Harvey, I.: Fifth Annual Symposium on Antibiotics, Washington, D.C., Oct. 2-4, 1957. 12. Trafton, H. M., and Lind, H. E.: *Ibid.* 13. Welch, H., Lewis, C. N., Staffa, A. W., and Wright, W. W.: Ant. Med. & Clin. Ther. 4:215, 1957.

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TETREX Capsule

Tetracycline phosp complex—each ca equivalent to 250 tetracycline HCl ac

TETREX Pediatric Capsul

Tetracycline phosp complex—each ca equivalent to 100 tetracycline HCl ac

TETREX Intramuscular '2 with Xylocaine

Tetracycline phosp complex—each vial alent to 250 mg. te cline HCl activity.

TETREX Intramuscular '1 with Xylocaine

Tetracycline phosp complex—each vial alent to 100 mg. te cline HCl activity.

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Tetracycline (phosp buffered) Syrup – 5-cc. tsp. equivale 125 mg. tetracycline activity.

TETREX Pediatric Drop

Tetracycline (phosp buffered) Syrup – cc. equivalent to 10 tetracycline HCl ac

TETREX-APC wi BRISTAMIN® Caps

Tetracycline phosp complex — each ca equivalent to 125 m racycline HCl activity phenyltoloxamine APC.

Available for y prescription at leading pharma

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IN OBSTETRICS IN MINOR SURGERY IN PEDIATRICS

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Brand of trichloroethylene U.S.P. (Blue)

"Duke"® University Inhaler

No. 3160 Model-M

• *notably safe and effective*

"Trilene," self administered with the "Duke" University Inhaler, under proper medical supervision, provides highly effective analgesia with a relatively wide margin of safety.

• *convenient to use*

The "Duke" University Inhaler (Model-M) is specially designed for economy, facility of handling, and ready control of vapor concentration.

• *special advantages*

Induction of analgesia is usually smooth and rapid with minimum or no loss of consciousness. Patients treated on an ambulatory basis can usually leave the doctor's office or hospital within 15 to 20 minutes. Inhalation is automatically interrupted if unconsciousness occurs.

"Trilene" *alone* is not recommended for anesthesia nor for the induction of anesthesia. Epinephrine is contraindicated when "Trilene" is administered.

"Trilene" is available in 300 cc. containers.

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a significant
advance
in the relief
of pain
and the
shortening of labor
in childbirth.

Cervilaxin

NATIONAL brand of relaxin

for shorter labor,
...easier delivery

Answers to some questions on Cervilaxin[1,2]

Q. What is Cervilaxin?

A. Cervilaxin is a new, highly purified form of relaxin, a hormone normally produced at term.

Q. When is it indicated?

A. Cervilaxin is of value in frank labor with slow cervical dilatation, and, with oxytocin, for induction of labor and uterine dysfunction.

Q. What are its advantages?

A. Cervilaxin eases and shortens labor (see Fig. 1): less pain, less trauma, less need for intervention. It lessens danger of fetal damage (brain injury).

Cervilaxin makes oxytocin safer since there is less likelihood of uterine rupture or other adverse effects.

Q. How does it act?

A. Cervilaxin softens the cervix so that it offers less resistance to passage of the fetus; dilatation is facilitated.

Q. Is Cervilaxin recommended for controlling premature labor?

A. No. In massive doses Cervilaxin may retard uterine contractions and prevent premature birth, but this effect is not evident in the smaller doses recommended here.

Q. Is Cervilaxin indicated only in primiparas?

A. No, Cervilaxin has been used with good results in primiparas, and in multiparas with a history of previous difficult labor.

Q. Does Cervilaxin interfere with necessary uterine contractions during labor?

A. No. In recommended dosage there is no interference with well established, regular and normal physiological functions before, during, or after delivery.

Q. What effect does Cervilaxin have on other drugs given during delivery?

A. Cervilaxin does not interfere with the action of any of the drugs commonly employed before, during, or after delivery.

Q. What side effects have been observed?

A. To date, none.

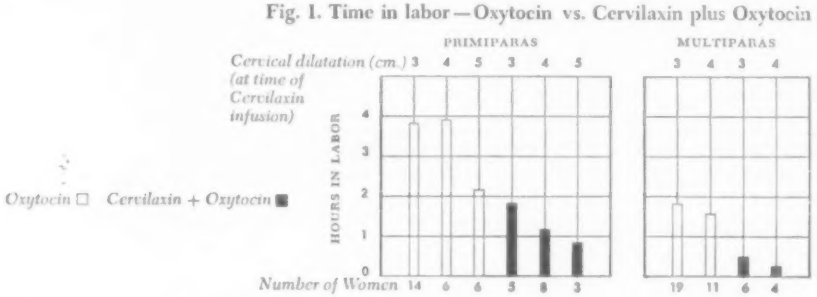
Q. How is Cervilaxin administered?

A. By intravenous drip.

Q. What is the dose?

A. Cervilaxin is supplied in 2 ml. vials containing 20 mg./ml. Usually this one dose is sufficient. Complete dosage and administration instructions are in the package literature.

Fig. 1. Time in labor—Oxytocin vs. Cervilaxin plus Oxytocin



1. Adapted from Birnberg, C. H. and Abitbol, M. M.: Refined Relaxin and Length of Labor, Obst. & Gynec., in press.
2. Eisenberg, L.: Facilitation of Full-Term Labor with Relaxin, in press.

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Pet Milk Company is proud to introduce new PET *Instant* to the medical profession.

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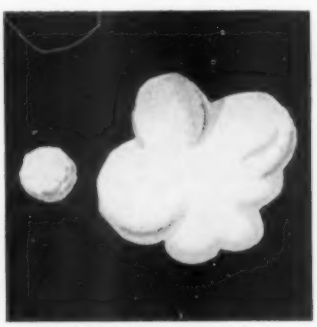

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Your patients pay no more for the added benefits of FILIBON

Each capsule contains:

Vitamin A	4,000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	3 mg.
Pyridoxine (B_6)	1 mg.
Niacinamide	10 mg.
Riboflavin (B_2)	2 mg.
Vitamin B_{12}	2 mcgm.
Ascorbic Acid (C)	50 mg.
Vitamin K (Menadione)	0.5 mg.
Folic Acid	1 mg.
Ferrous Fumarate	90 mg.
Iron (as Fumarate)	30 mg.
Intrinsic Factor	5 mg.
Fluorine (as CaF_2)	0.015 mg.
Copper (as CuO)	0.15 mg.
Iodine (as KI)	0.01 mg.
Potassium (as K_2SO_4)	0.835 mg.
Manganese (as MnO_2)	0.05 mg.
Magnesium (as MgO)	0.15 mg.
Molybdenum (as $Na_2MoO_4.2H_2O$)	0.025 mg.
Zinc (as ZnO)	0.085 mg.
Calcium Carbonate	575 mg.

Dosage: one or more capsules daily.

Supplied: attractive, re-usable bottles of 100 capsules.

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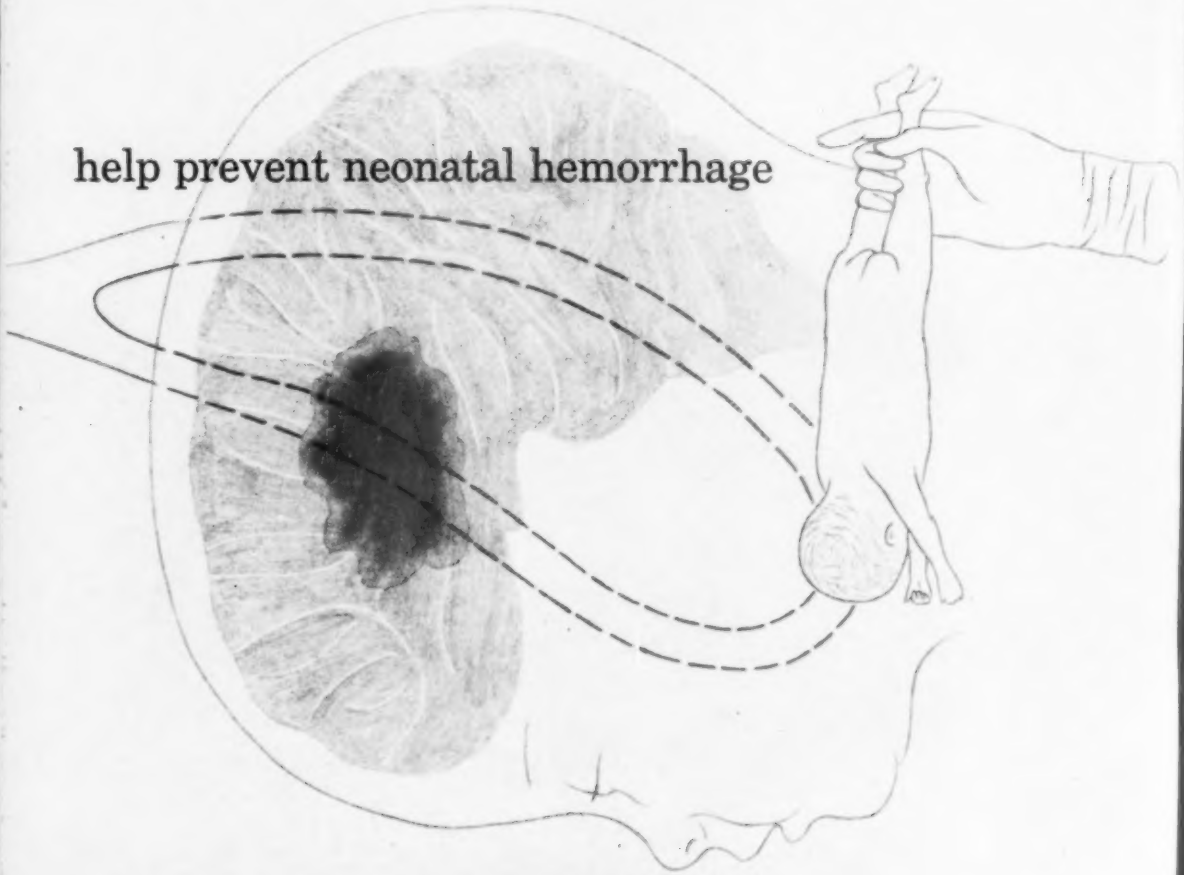
help prevent neonatal hemorrhage



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VITAMIN K_1

the only available preparation chemically identical with naturally-occurring vitamin K_1 . . .

*"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"**

- helps prevent "physiologic" hypoprothrombinemia, the most probable cause of hemorrhagic disease of the newborn
- helps reduce incidence of intracranial hemorrhage at birth
- if 'Mephyton' has not been given to the mother before delivery, it can be administered to the infant if birth is premature, if surgery is necessary, or if treatment of neonatal hemorrhage is required

Dosage: Hemorrhagic disease of the newborn, 0.5 to 2 mg. prophylactically to the mother is usually adequate; if actual hemorrhage occurs, up to 10 mg., repeated if necessary, may be given to the newborn.

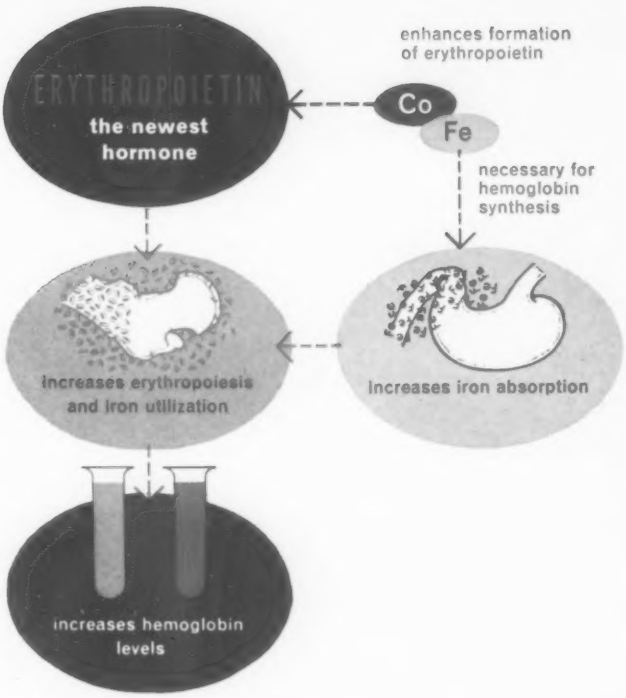
Supplied: Tablets, 5 mg., bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg., boxes of 6 ampuls.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA

Mephyton is a trade-mark of MERCK & CO., INC.

*Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 50

NEW RESEARCH ON ERYTHROPOIETIN EXPLAINS CLINICAL SUPERIORITY OF



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Elucidation of the action of erythropoietin—the erythropoietic hormone—provides a clear explanation for the observations of Holly,[1] Ausman,[2] Tevetoglu[3] and many others who have reported that in the common anemias cobalt-iron therapy results in a clinical response superior to that produced by iron alone.

Increased Iron Absorption and Utilization—Recent investigations show that cobalt enhances the formation of erythropoietin.[4,5] This hormone increases the rate of production of new red cells which, in turn, increases the rate of both iron utilization by the marrow and iron absorption from the intestine.[6]

Clinical Application—In simple *iron deficiency anemia*, 89% of patients treated with Roncovite exceeded 12 Gm. of hemoglobin per 100 cc., while only 33% of the same patients treated with iron alone for a comparable period reached this level.[2] In *anemia of pregnancy*, 98.2% of Roncovite-treated patients maintained their hematologic status; 63.8% delivered with a hemoglobin of 13 Gm. per 100 cc. or more.[1] In *anemia of infancy and childhood* an average hemoglobin level of only 8.7 Gm. per 100 cc. was attained with iron alone while the same patients subsequently reached an average hemoglobin level of 11.6 Gm. per 100 cc. with Roncovite.[3]

Roncovite-MF is the new therapeutic agent based on erythropoietin formation which translates this new research into the practical utility of full iron effectiveness with greatly decreased, better tolerated iron dosage.

Each enteric-coated, green tablet contains:

Cobalt chloride, 15 mg.
Ferrous sulfate exsiccated, 100 mg.

Maximum adult dosage:

one tablet after each meal and at bedtime.
Supplied: Bottles of 100 tablets.

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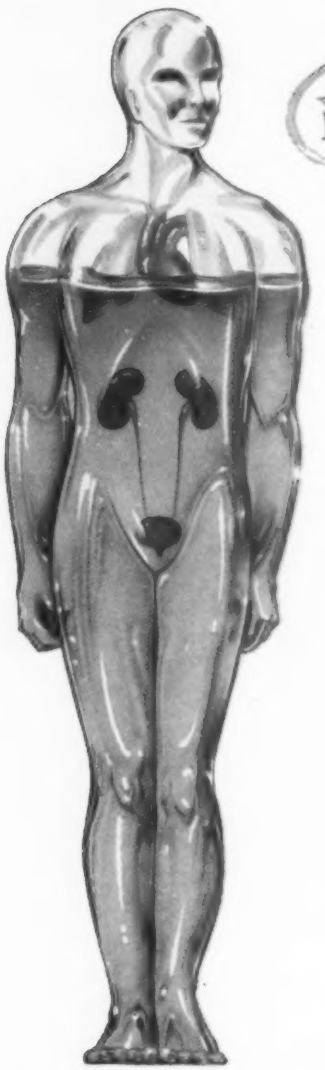

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Edema and Hypertension

EDEMA

1. 'DIURIL' is an entirely new, orally effective, nonmercurial agent—1 Gm. of 'DIURIL' orally being approximately equivalent to 1 cc. of mercurial I.M.
2. 'DIURIL' is ideal for initiating diuresis and for prolonged maintenance of the edema-free state.
3. 'DIURIL' promotes the balanced excretion of sodium and chloride without producing acidosis.
4. 'DIURIL' offers a rapid rising response to increased doses (within recommended dosage range).
5. 'DIURIL' is well tolerated even at maximum therapeutic doses.
6. 'DIURIL' acts rapidly (onset within 2 hours) and its moderate duration of action (6-12 hours) permits uninterrupted rest at night.
7. 'DIURIL' has no known contraindications.

any indication for diuresis is an indication for 'DIURIL'

INDICATIONS: Congestive heart failure; premenstrual edema; edema of pregnancy; renal edema—nephrosis, nephritis; cirrhosis with ascites; drug-induced edema. May be of value to relieve fluid retention complicating obesity.

DOSAGE RANGE: one 500 mg. tablet 'DIURIL' to two 500 mg. tablets 'DIURIL' once or twice a day.

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1. 'DIURIL' provides basic therapy to improve and simplify the management of hypertension.
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4. 'DIURIL' maintains its effectiveness even during prolonged therapy.
5. 'DIURIL' smooths out blood pressure fluctuations.
6. 'DIURIL' is orally administered with simple dosage schedules.

INDICATIONS: Hypertension of all degrees of severity.

DOSAGE RANGE: one 250 mg. tablet 'DIURIL' two times daily to one 500 mg. tablet 'DIURIL' three times daily.

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SUPPLIED: 250 mg. and 500 mg. scored tablets of 'DIURIL' (Chlorothiazide); bottles of 100 and 1,000.

BIBLIOGRAPHY: Baer, J. E. *et al.*: *Fed. Proc.* **16**:278, (March) 1957; Beyer, K. H. *et al.*: *Fed. Proc.* **16**:282, (March) 1957; Ford, R. V. *et al.*: *M. Rec. & Ann.* **51**:376, (April) 1957; Ford, R. V. *et al.*: *Arch. Int. Med.* **100**:582, (October) 1957; Ford, R. V. *et al.*: *Antibiotic Med. & Clin. Therapy* (in press); Moyer, J. H. *et al.*: *Proc. Soc. Exper. Biol. & Med.* **95**:529, (July) 1957; Novello, F. C. and Sprague, J. M.: *J. Am. Chem. Soc.* **79**:2028, (April 20) 1957; Russo, H. F. *et al.*: *Fed. Proc.* **16**:333, (March) 1957; Hollander, W. and Wilkins, R. W.: *Boston Med. Quart.* **8**:69, (Sept.) 1957; Freis, E. D. *et al.*: *J.A.M.A.* (in press); Finnerty, F. A.: *N. Y. State J. Med.* **57**:2957, (Sept. 15) 1957; Freis, E. D. and Wilson, I. M.: *Med. Ann. District of Columbia* **26**:468, (Sept.) 1957; Freis, E. D. *et al.*: *Circulation* (in press).

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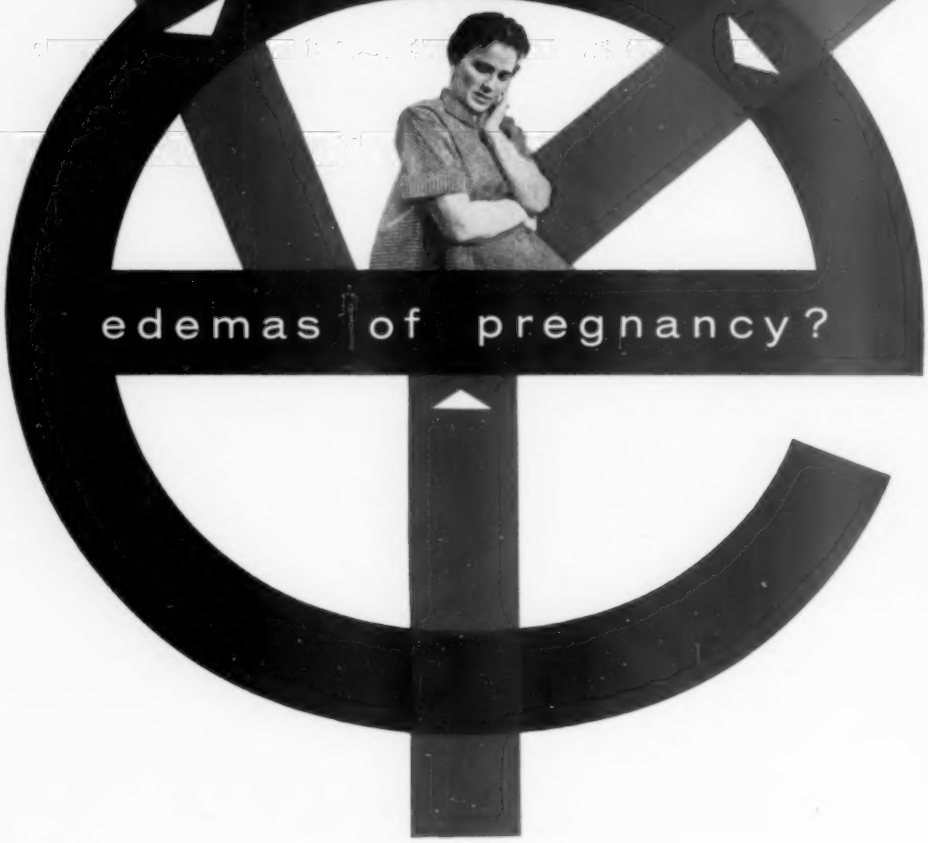

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1. Brit. M. J. *1*:1007, 1953
2. Brit. M. J. No. 4896, 1071, 1954.
3. Am. J. Obst. & Gynec. *74*:1054, Nov., 1957.

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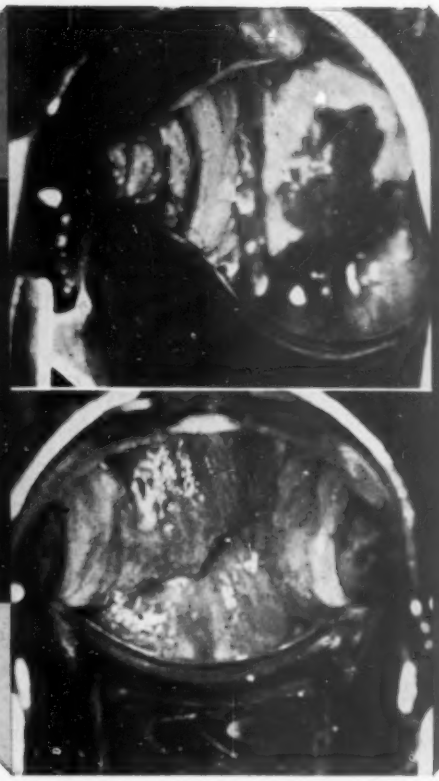

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1. Thomas, H. H.: Obstet. & Gynec. 9:163, 1957. 2. Browne, A. D. H.: J. Irish M.A. 40:86, 1957. 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268, 1956.

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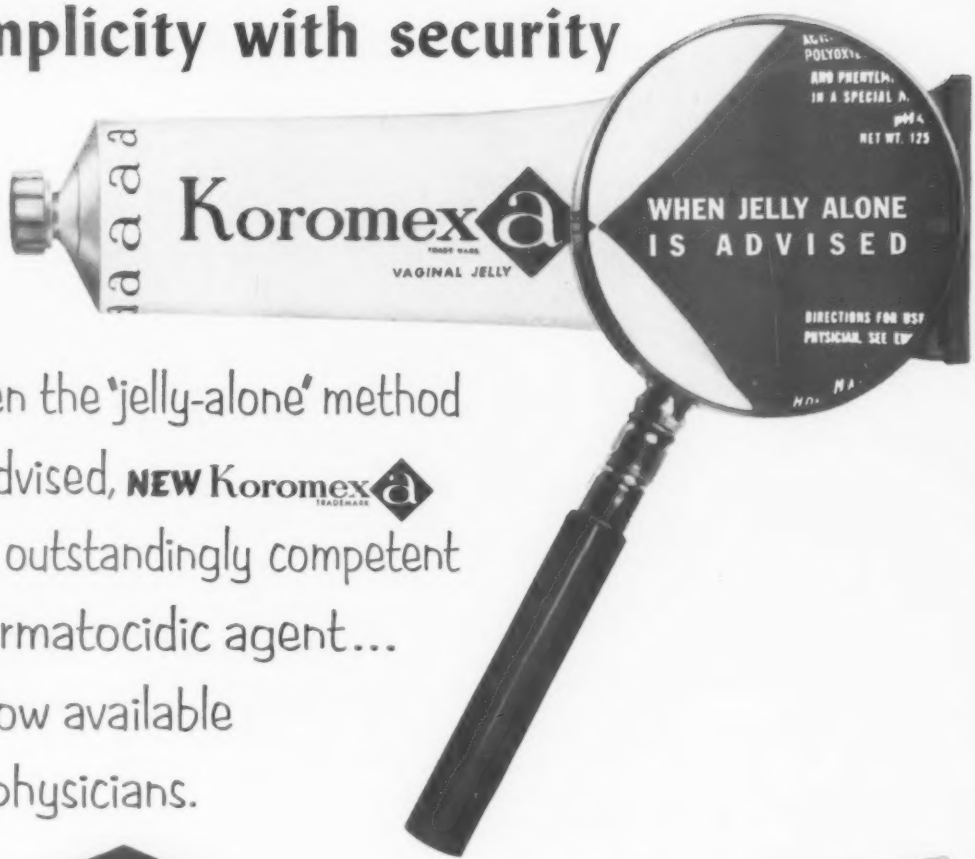

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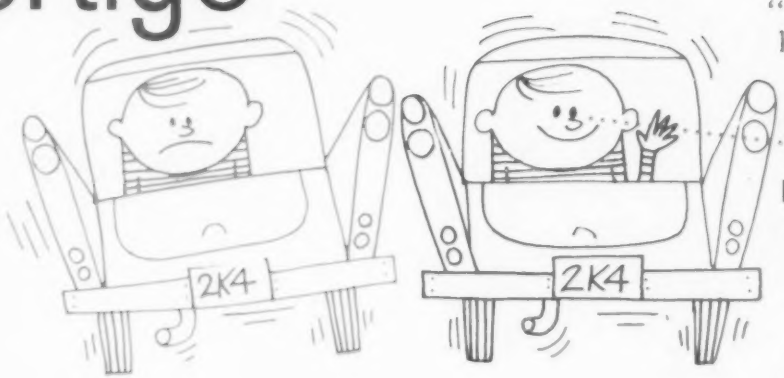

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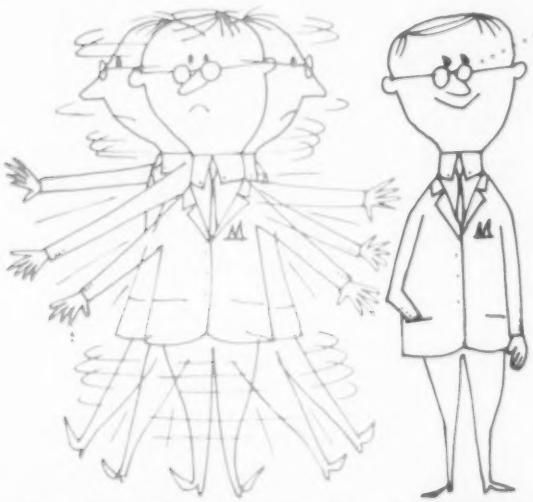

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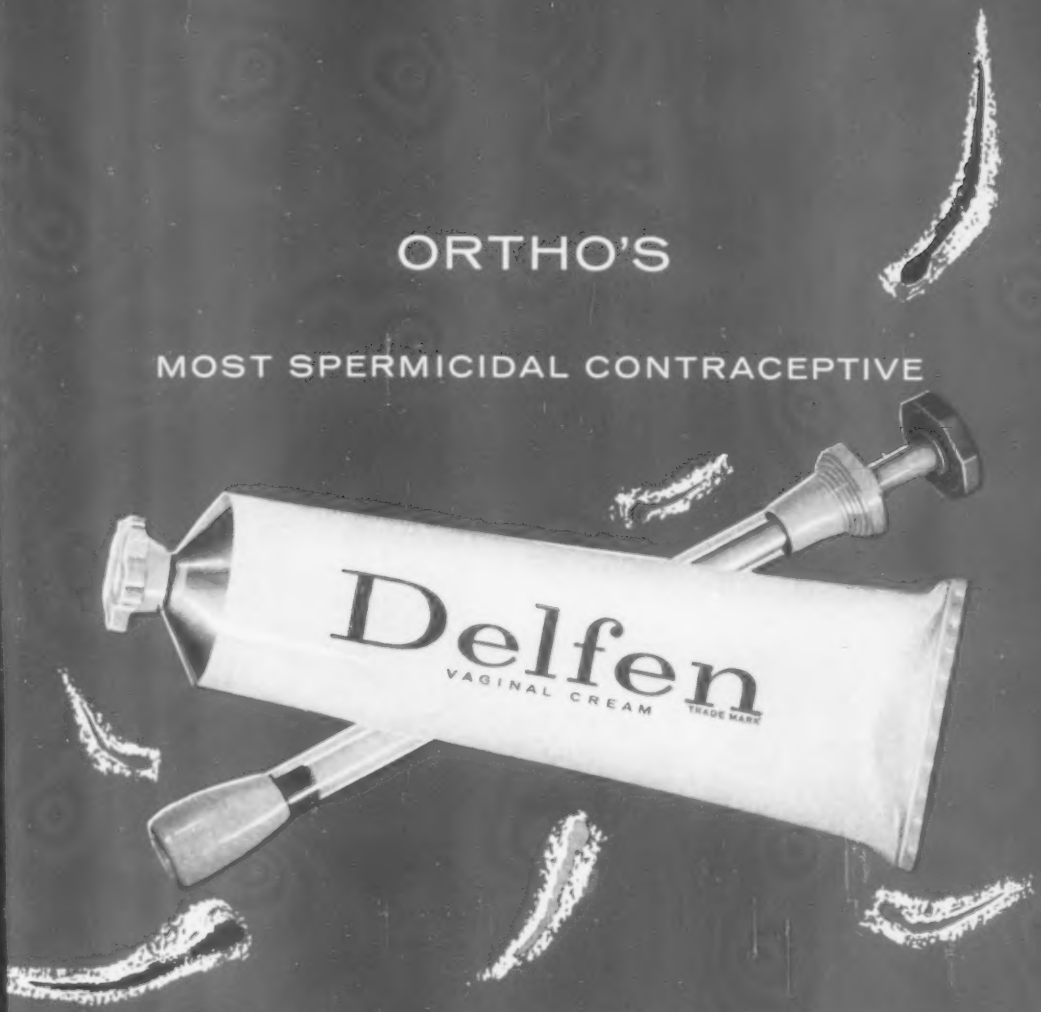

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A bibliography is given after each chapter. While in no sense can it be regarded as complete, the references included are those which the authors feel are valuable.

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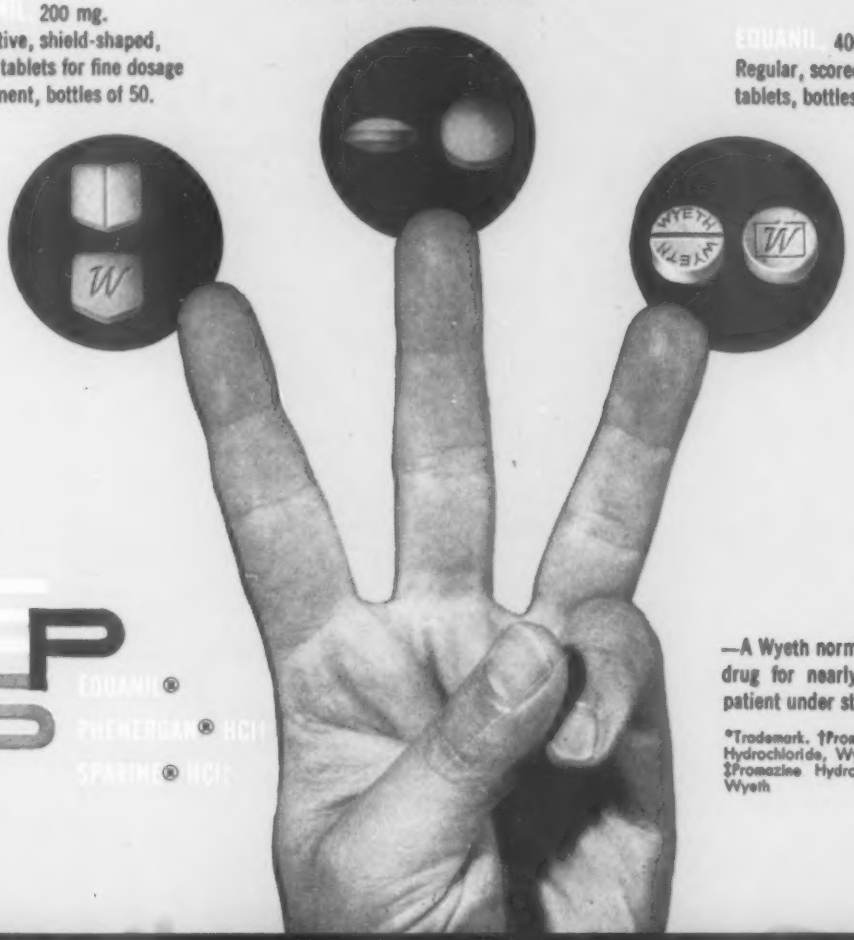

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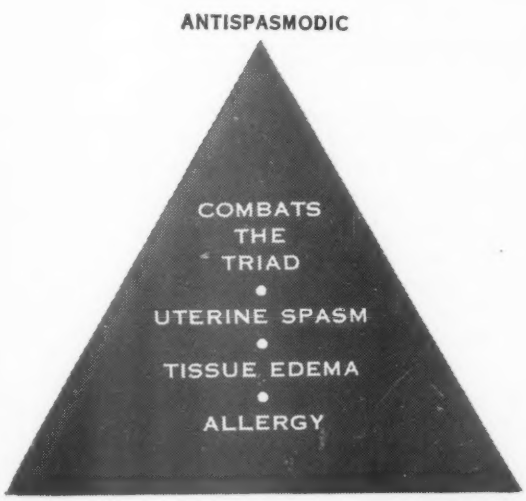

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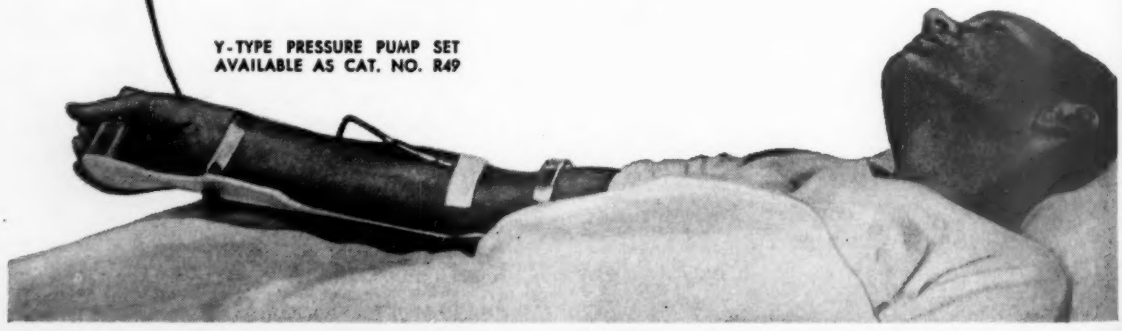

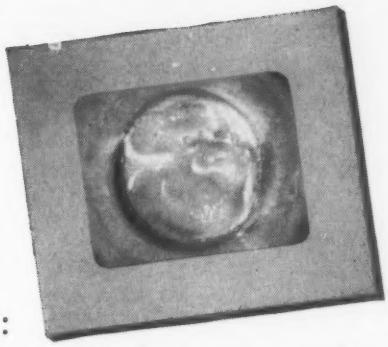

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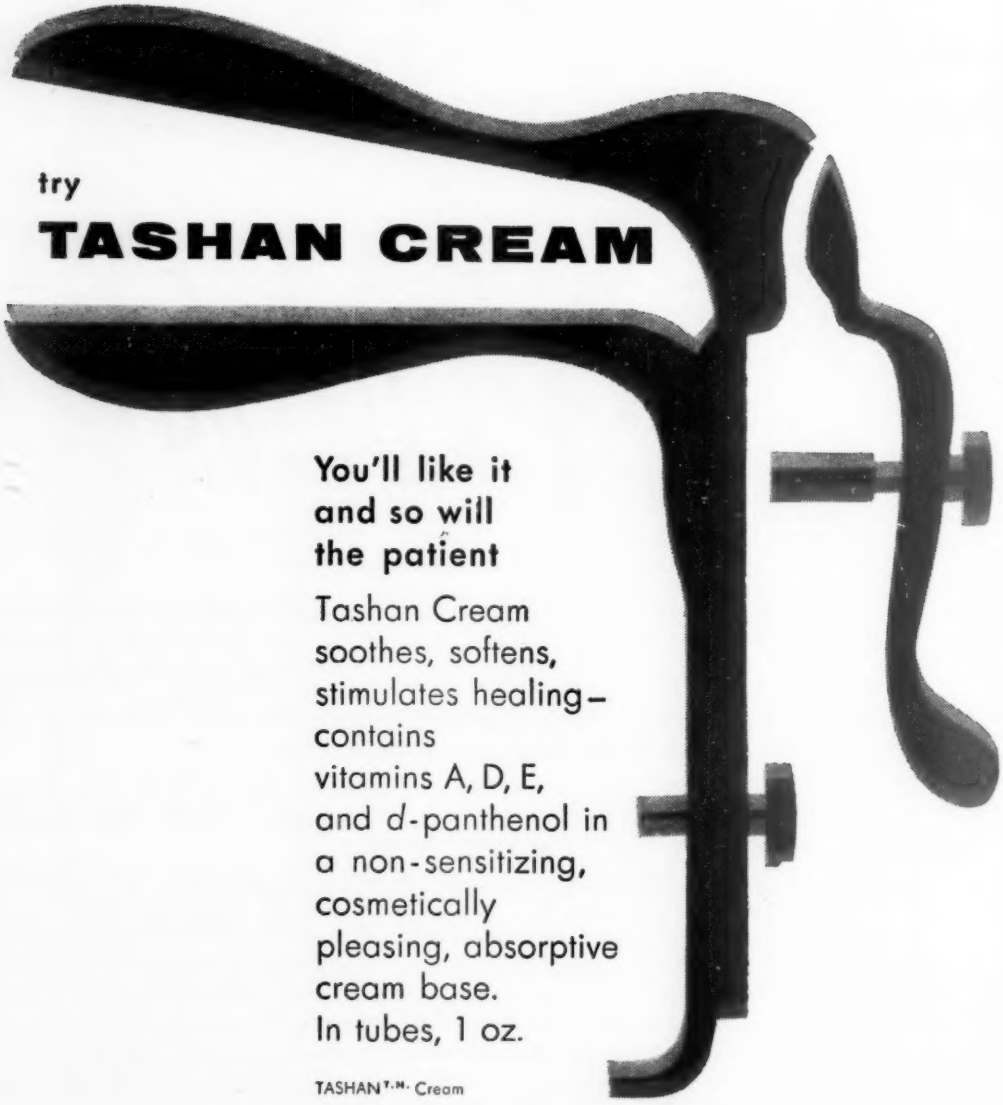

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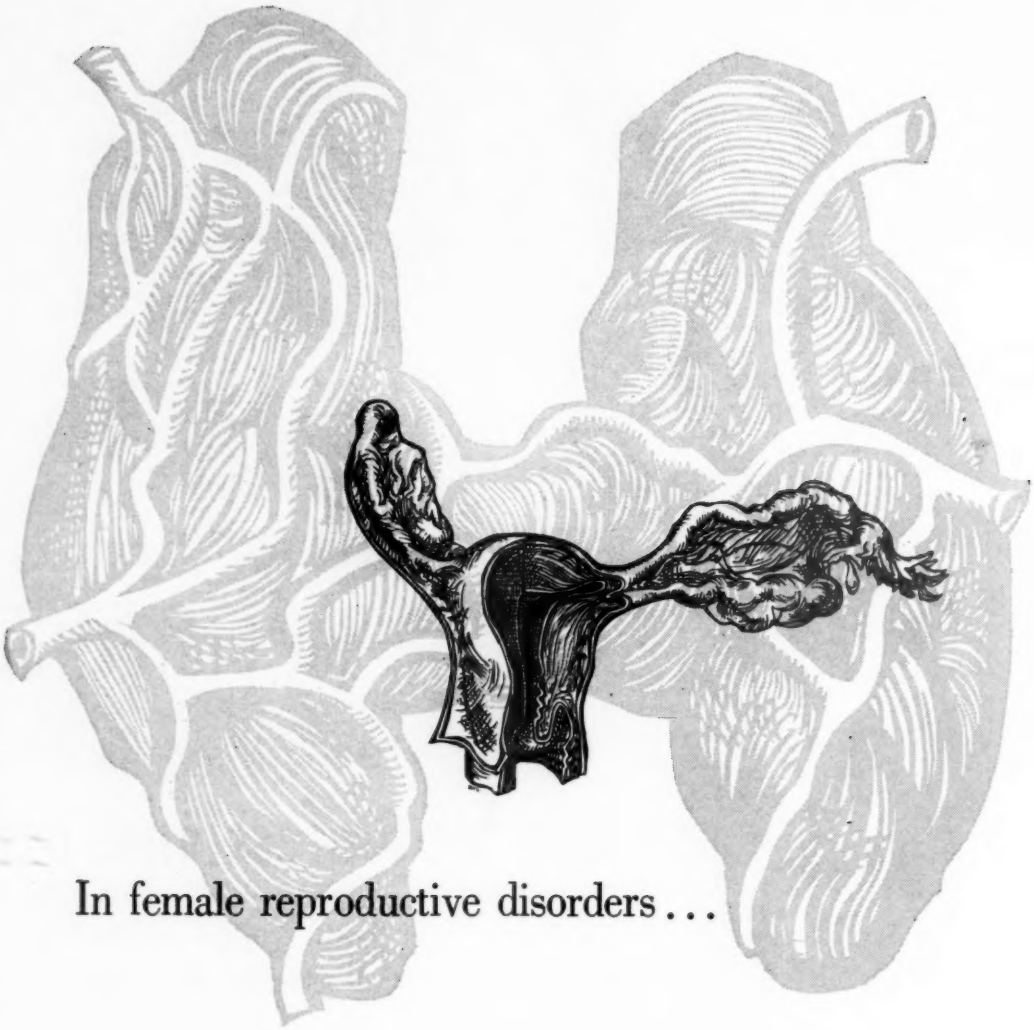

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1. Kupperman, H.S.: Amenorrhea: Diagnosis and Therapy, Surg. Clin. North America, April, 1957, p. 517.

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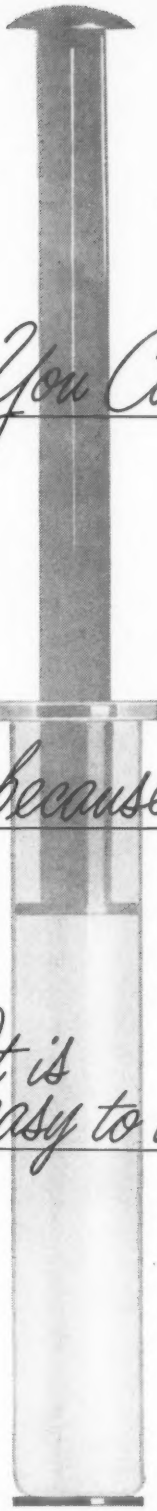

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OBSTETRICS AND GYNECOLOGY

Gynecology

THE RELATION OF NONMALIGNANT POSTMENOPAUSAL ENDOMETRIAL CHANGES TO OVARIAN MORPHOLOGY*

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IN A PREVIOUS study,[7] an attempt was made to correlate the presence or absence of ovarian stromal hyperplasia with endometrial carcinoma. We found no such correlation and thus were unable to confirm the findings of previous workers.[2, 5, 8, 9]

It has been postulated that "ovarian stromal hyperplasia" is perhaps responsible for the production of estrogen. The estrogen in turn is thought to be responsible for the development of endometrial activity and ultimately carcinoma. The present study is a re-examination of our data to see if there was a correlation between these ovarian changes and findings in nonmalignant endometrium indicative of estrogen stimulation. If such correlation were found, then one could postulate that estrogen was, in fact, being produced in those individuals with "ovarian stromal hyperplasia" and in sufficient quantity to stimulate the endometrium.

Summary of Literature

The literature either implicating or exonerating excessive estrogen stimulation as a cause of endometrial hyperplasia followed by endometrial adenocarcinoma is vast. These articles were reviewed by Larson[3] in some detail while at work in our laboratory in 1954, and their inclusion here would seem redundant.

*Aided by a grant from the Service League of Chicago Wesley Memorial Hospital and financed in part by a cancer control grant from the National Cancer Institute of the National Institutes of Health of the Department of Health, Education and Welfare.

Two recent articles in the British literature should be mentioned. McBride[4] studied the uninvolved endometrium, myometrium, vulva, vagina, cervix, and tubes in postmenopausal women with and without endometrial carcinoma. He found no significant differences in the two groups. Bamforth,[1] on the other hand, presented 81 cases, 22 of which had uninvolved endometrium available for study. Of this group 5 were atrophic and 17 showed endometrial hyperplasia, by his criteria. He gave no ages in his report.

In the various articles on "ovarian stromal hyperplasia," there has been no attempt to correlate its presence or absence with the status of the nonmalignant endometrium. In fact, it has not yet been shown that these ovarian changes actually do produce estrogen, a fact pointed out by Emil Novak[6] in a discussion of one of the studies dealing with cancer and "ovarian stromal hyperplasia."

Material and Methods

This study includes 63 of the original 82 cases studied. In 17 of the 19 omitted, there was carcinoma of the endometrium with no available uninvolved endometrium, and 2 were from the control group. These latter 2 cases were omitted because the patients were not yet one year past the menopause, and so were not pertinent to this discussion. The age distribution of the patients is seen in Table I.

TABLE I. AGES OF PATIENTS IN SERIES

AGE RANGE	NO. OF CASES
40-44	2
45-49	5
50-54	19
55-59	9
60-64	17
65-69	8
70-74	3

The tissue was obtained from two sources, the files of the departmental laboratory and fresh operating room specimens. The latter accounted for most of the noncarcinoma group, the operation being done for pelvic relaxation or other benign conditions. New sections were cut from all blocks and adjacent sections of ovary were stained with hematoxylin and eosin, the Milligan trichrome stain, and the Wilder reticulum stain. Sections from the uterus were stained with hematoxylin and eosin.

The following specific morphologic details in the ovary were studied: cortical granulomas, germinal inclusion cysts, thecosis, hilar cells, and the relative amount of collagen present. This latter is clearly delineated in the trichrome stains. Criteria for defining these entities have been previously recorded.[7] The number of reticulum fibers present has been omitted from our tables as it was found to be inversely proportional to the amount of collagen.

Ultimately, the endometrial pattern was classified either as inactive or active. The inactive endometria included those showing atrophy, with and without cystic change, and inactive or regressing hyperplasia. Endometria were considered active if they showed either endometrial hyperplasia or physiologic proliferative change. Atrophy was characterized by a paucity of endometrial glands and stroma, as well as an absence of mitotic figures. In roughly one-third of these cases, cystic dilatation of some glands was noted. Endometrial hyperplasia was recognized by an increase in thickness of the endometrium with increase in the number of glands and the amount of stroma, frequent mitotic figures, and frequent cystically dilated glands of

variable size. Inactive hyperplasia was judged to be present when the endometrium was thicker than normal, but the stromal cells were loosely arranged and the glands, although frequently cystic, were lined by a low inactive epithelium with no mitotic figures. The usual criteria for proliferative endometrium were used.

The slides were studied by both authors independently and the results compared. Slides in which there was a difference of opinion were then reexamined, and a mutually satisfactory conclusion was drawn.

Results

Table II gives a summary of the findings. The number of each type of endometrium is tabulated according to the respective ovarian findings. Table III is a summary of Table II using the two large endometrial groups, active and inactive. The only ovarian findings that appear more often in one group than the other are thecosis and germinal inclusion cysts. Interestingly, these two ovarian findings are more common in the inactive group. However, the difference in incidence is not significant at a 5 per cent level. The other ovarian changes studied do not vary sufficiently from one group to another to warrant mention.

TABLE II. TABULATION OF RESULTS OF ALL CATEGORIES

	NO. OF CASES	HILAR CELLS	THECOSIS	CORTICAL GRANULOMA	GERMINAL INCLUSION CYSTS	COLLAGEN		
						SLIGHT	INTERMEDIATE	MARKED
Atrophic	48	16	13	20	35	9	36	3
Inactive hyperplasia	4	2	2	4	3	0	3	1
Hyperplasia	7	3	1	3	3	0	7	0
Proliferative	4	1	0	2	3	0	4	0
Total	63	22	16	29	44	9	50	4

TABLE III. SUMMARY OF RESULTS

	NO. OF CASES	HILAR CELLS		THECOSIS		CORTICAL GRANULOMA		GERMINAL INCLUSION CYSTS		COLLAGEN					
										SLIGHT		INTERMEDIATE		MARKED	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
No activity	52	18	34.6	15	28.8	24	45.9	38	73.1	9	17.3	39	75	4	7.7
Activity	11	4	36.3	1	9	5	45.4	6	54.5	0	-	11	100	0	
Total	63	22	34.7	16	25.4	29	46	44	69.5	9	14.3	50	79.3	4	6.3

Some of the findings in this report are at variance with those observed in another study performed in our departmental laboratory on the normal postmenopausal endometrium, in that the incidence of "activity" herein reported is higher. In the present study, 17 per cent of the endometria showed some activity whereas in the study of normal endometria previously mentioned the incidence was less than 2 per cent. The study of normal postmenopausal endometrium was restricted to tissue from women who were at least 2 full years postmenopausal, who had had no bleeding, and who had not received exogenous estrogen.

Table IV summarizes the data from the patients in the present study with endometrial activity. It can be seen that in only 2 instances (Nos. 8443 and 21023) are the conditions comparable to those in the previously mentioned group of "normals." We believe that the differences in the criteria necessary

TABLE IV. HISTORY AND FINDINGS IN PATIENTS WITH "ACTIVE" ENDOMETRIA

LABORATORY NO.	AGE	CARCINOMA	NONMALIGNANT ENDOMETRIUM	YEARS SINCE LAST MENSTRUAL PERIOD	REASON FOR OPERATION	PREOPERATIVE HORMONES	THECOSIS	HILAR CELLS	CORTICAL GRANULOMA	GERMINAL INCLUSION CYSTS	COLLAGEN
21187	68	No	Prolif.	15	Prolapse	Yes	0	+	0	+	I*
10396	52	No	Prolif.	2½	Pain. Fibroids	Yes	0	0	+	+	I
21023	53	No	Prolif.	3	Fibroids	No	0	0	+	+	I
21447	62	No	Hyper.	25	Prolapse	Yes	0	0	0	0	I
8443	74	No	Hyper.	25	Vaginal discharge	No	0	0	0	+	I
21868	57	No	Hyper.	1½	Vaginal bleeding	No	+	+	+	0	I
22529	52	Yes	Prolif.	1	Vaginal bleeding	No	0	0	0	0	I
12442	61	Yes	Hyper.	5	Vaginal bleeding	No	0	0	+	0	I
22615	65	Yes	Hyper.	15	Vaginal bleeding	No	0	+	0	0	I
21739	54	Yes	Hyper.	3	Vaginal bleeding	No	0	0	0	+	I
21663	65	Yes	Hyper.	20	Vaginal bleeding	No	0	+	+	+	I

*Intermediate in amount.

for inclusion in the two series account for the differences in results. The patients who received hormones were given the equivalent of 0.5 mg. of stilbestrol daily for one to 2 weeks before vaginal surgery in order to facilitate dissection.

Summary and Conclusions

1. The morphologic changes in the ovary, which collectively are considered by some to be diagnostic of "ovarian stromal hyperplasia," have been tabulated with the findings in the nonmalignant endometria of 63 postmenopausal women.

2. These ovarian changes were neither more nor less commonly found in patients who showed "active" or "inactive" endometrium to an extent approaching statistical significance.

3. This lack of correlation seems to indicate that these changes are not accompanied by increased estrogen secretion, at least not in amounts sufficient to stimulate the endometrium.

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CYCLICAL CHANGES OF ELECTROLYTES IN ENDOMETRIAL TISSUE*

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THE histologist has long noted the appearance of endometrial stromal edema, which occurs cyclically at two stages in the human menstrual cycle. Noyes, Hertig, and Rock[1] described this edema as varying in degree with the individual. This is particularly true of the proliferative phase edema, seen usually between days 6 and 12, with a peak (which in some cases may be almost absent) at about days 8 to 9. They noted that the edema of the secretory phase, which is seen usually between days 19 and 26, with a peak at about days 22 to 23, is greater in extent and more constant.

In view of the limited investigation of this phenomenon, the assumption has apparently been made that this is a true edema, that water and electrolytes move into the intercellular spaces with the appearance of the edema, and then move out again as it recedes. Determinations of per cent water content have raised some question as to the validity of this assumption.

Van Dyke and Chen,[2] in the monkey, and Astwood,[3] in the rat, have shown that the water content of the uterus varies cyclically. Water content was found to be highest during the period of follicle ripening, or after exogenous estrogen, lower during the period of corpus luteum function, and, in the monkey, lowest during menstruation, or after ovariectomy. Thus it seemed that estrogen was an important factor in uterine hydration. Since these studies included both myometrium and endometrium, however, no conclusions can be drawn as to cyclical changes in endometrial hydration.

Studies of human endometrium have shown a similar cyclical variation in water content. Stuermer and Stein[4] determined the water content of endometrial biopsy specimens obtained from 6 healthy women weekly throughout a single cycle. Their method included a preweighing immersion in a Krebs-Ringer's-phosphate solution, which may have resulted in some distorted values, since it has been shown[5] that isolated parenchymatous tissue, though not specifically endometrium, takes up water when soaked in isotonic media. Their data showed that the average value for per cent water content during the early proliferative phase was 1 per cent higher than the average values for the late proliferative phase, or late secretory phase, with the average water lowest during the early secretory phase. They felt that their data were too few for statistical

*This project was supported in part by a research grant from the Josiah Macy, Jr., Foundation.

analysis, but that apparently there was no significant cyclical variation in the water content of human endometrium. They did conclude that there was no evidence to support the secretory phase edema theory of the histologist.

McLennan and Koets[6] studied the water content of human endometrium obtained from hysterectomy specimens. Their results showed a definite peak in water content in the midproliferative phase. They described a possible minor rise about days 22 to 24, but again there was no evidence to support a secretory phase edema. The mean difference in water content between tissues from days 6 to 12, the period of proliferative phase edema, and tissues from days 19 to 26, the period of secretory phase edema, is statistically significant to greater than 99.9 per cent as measured by the "t" test (applied by this author).

In view of this apparent contradiction between histological picture and water content, it was felt that a re-examination of cyclical endometrial hydration should be carried out, and in addition possible cyclical changes in endometrial electrolyte content should be investigated.

Material and Methods

Material was obtained from such hysterectomy specimens as could be expected to have normal endometrium. Most of the women had had fairly regular 26 to 30 day menstrual cycles. In the majority of cases operation was performed for leiomyomas of the uterus, but 3 of the specimens were removed for early carcinoma of the cervix.

Specimens were obtained from one to 3 hours after operation. The endometrium was removed by scraping with a scalpel. The tissue was immediately blotted lightly on filter paper to remove any surface blood or serum. An attempt was made to obtain approximately 0.5 gram of tissue, but wet weights varied from about 0.2 to 1.0 gram. Care was taken to exclude hemorrhagic areas, as well as areas distorted by leiomyomas.

The tissue was weighed immediately on an analytical balance, and dried to a constant weight (for about 24 hours) in a vacuum oven at 100 to 110° C. and approximately one-third atmosphere pressure. Dry weight was obtained, and the specimen was extracted with ethyl ether in a Soxhlet extractor for 24 hours to remove lipid material. The latter procedure was carried out because fat has been shown to vary throughout the menstrual cycle.[6] For this reason electrolyte concentrations are expressed in terms of dry, fat-free weight, and a more valid comparison among specimens obtained thereby.

Specimens were then digested in 3 ml. of concentrated nitric acid containing a known excess of silver nitrate. Digestion was achieved in 24 hours over a steam bath. The digest was filtered through a sintered glass disk into a 10 ml. volumetric flask, and the precipitate washed with 6 ml. of 1 per cent HNO_3. The solution was then made up to the volume of 10 ml.

A 2 ml. aliquot was used to determine chloride by the method of Van Slyke.[7] Aliquots of 6 and 1 ml. were submitted to flame photometry for determination of sodium and potassium, respectively.

The small amounts of tissue available made multiple determinations impossible. In a single specimen large enough for separate parallel determinations, water content agreement was within 1 per cent, as was the agreement of

the chloride determinations. The sodium determinations varied by 5 per cent and the potassium by 3 per cent. The variation in sodium and potassium is thought to have resulted from steps prior to the photometry, a sampling or handling error. Photometer operation showed less than 2 per cent error in repeated trial runs. The chloride titration error was estimated to be less than 3 per cent.

Serum electrolytes of the patients at the time of operation were determined for a number of the specimens. Subsequent computation of electrolyte spaces did not alter the findings significantly, and have not been included inasmuch as the various infusions the patients received on the operating table are felt to have made these figures of little or no value.

Dating of the tissue was carried out by the method of Noyes, Hertig, and Rock.[1] Accuracy was felt to be ± 2 days. Seventy per cent of the specimens were within 2 days of the clinically observed date. Some irregular cycles among the group may have occurred as a result of the psychic effect of impending surgery.

TABLE I. SUMMARY OF DATA IN 25 SPECIMENS OF ENDOMETRIUM

NO.	DAY	% WATER	ELECTROLYTES (MEQ./100 GRAMS FAT-FREE TISSUE)			Na:cl
			cl	Na	K	
1	2	79.1	33.6	43.8	38.5	1.30
2	6	83.8	77.8	94.9	50.3	1.22
3	6	81.8	72.6	110.0	55.9	1.51
4	7	87.0	68.2	80.3	43.3	1.18
5	8	86.3	75.5	110.1	88.9	1.47
6	9	86.0	74.0	97.1	63.3	1.54
7	9	84.9	78.1	96.2	59.5	1.24
8	11		76.4	95.5	49.0	1.25
9	11	78.8	73.7	87.6	52.5	1.19
10	11	83.8	73.3	90.0	44.7	1.23
11	17	85.2	59.3	63.9	46.6	1.09
12	19	80.5	47.2	61.6	40.3	1.30
13	20	84.9	60.9	76.6	42.0	1.26
14	20	83.7	54.5	63.5	48.9	1.17
15	22	81.2	45.2	52.7	45.9	1.17
16	23	85.5	63.0	69.4	50.5	1.10
17	24	82.7	47.8	54.2	48.4	1.13
18	25	84.7	43.8	54.7	45.2	1.25
19	26	84.6	56.9	69.9	46.8	1.23
20	26	85.5	65.3	73.4	41.9	1.13
21	26	83.0	36.9	55.8	41.6	1.51
22	27	83.8	38.3	55.7	51.1	1.45
23	27	81.1	39.2	56.0	36.7	1.43
24	27	81.7	46.4	55.8	36.9	1.20
25	28	83.0	34.4	60.4	43.0	1.76

Results

Twenty-five specimens were studied (Table I). No specimens fell in the period between days 12 and 16; however, there was a satisfactory distribution throughout the remainder of the menstrual cycle.

The data obtained for water content (Fig. 1) are roughly similar to those of McLennan and Koets.[6] The per cent of water varied from 78.8 to 87.0. The

average water content from day 6 to day 12 was 84.1 per cent as compared with 83.6 per cent for specimens from day 19 to day 26, a difference of 0.5 per cent. This difference is not statistically significant.

As can be seen in Fig. 2, potassium was somewhat higher on the average during the proliferative phase than during the secretory phase. This difference is statistically significant, to greater than 99.9 per cent as measured by the t test, and is in accord with previous observations of high potassium content in the presence of growth. Values varied from 36.7 to 59.5 mEq. per 100 grams

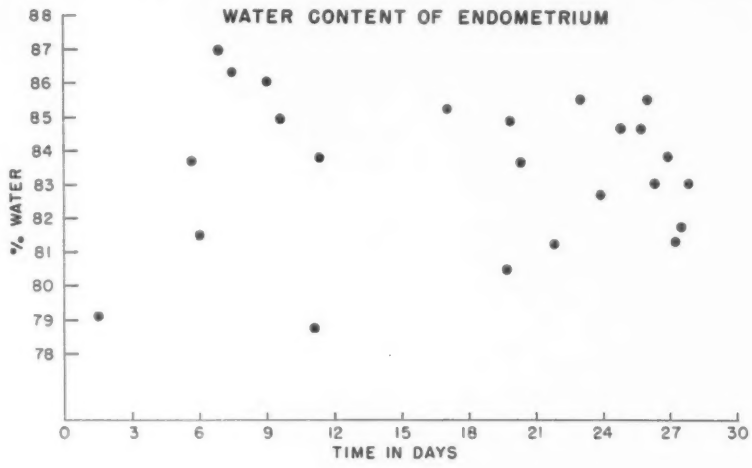

Fig. 1.

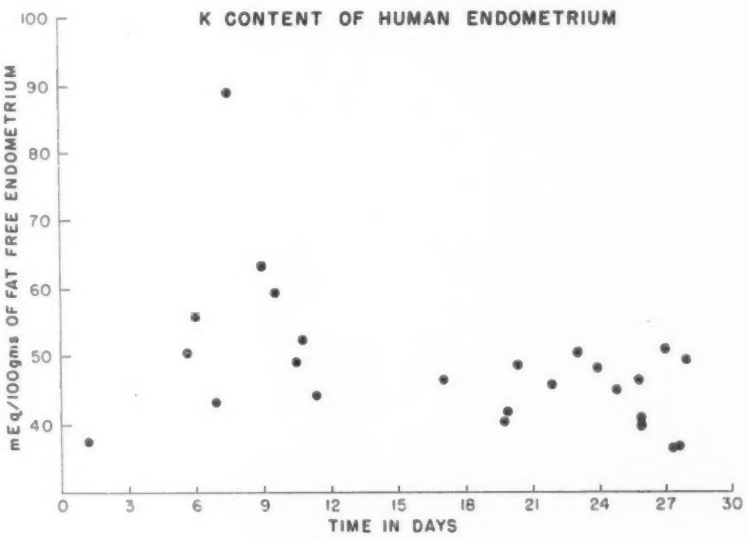

Fig. 2.

of dry, fat-free tissue, except for one value of 88.9 mEq., which may be an artifact, no doubt due to the inclusion of hemorrhagic areas in the specimen. This high value does not change the significance of the difference between the two phases, as measured by the t test.

The sodium and chloride data (Figs. 3 and 4) show significantly higher levels of these ions during the proliferative phase than during the secretory

phase. These differences are highly significant statistically as measured by the t test done on specimens of days 6 to 12 on the one hand, and of days 19 to 26 on the other. In the case of both ions there seems to be a gradual downslope from a peak in the early proliferative phase on into the secretory phase.

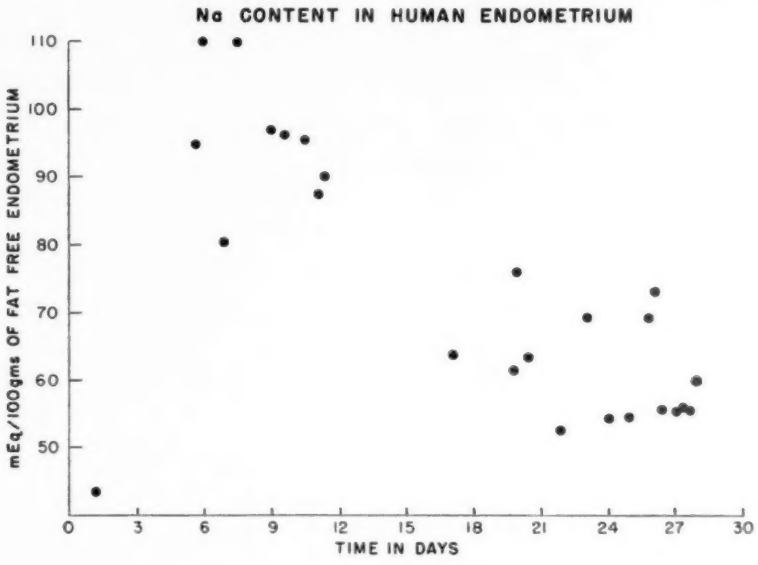

Fig. 3.

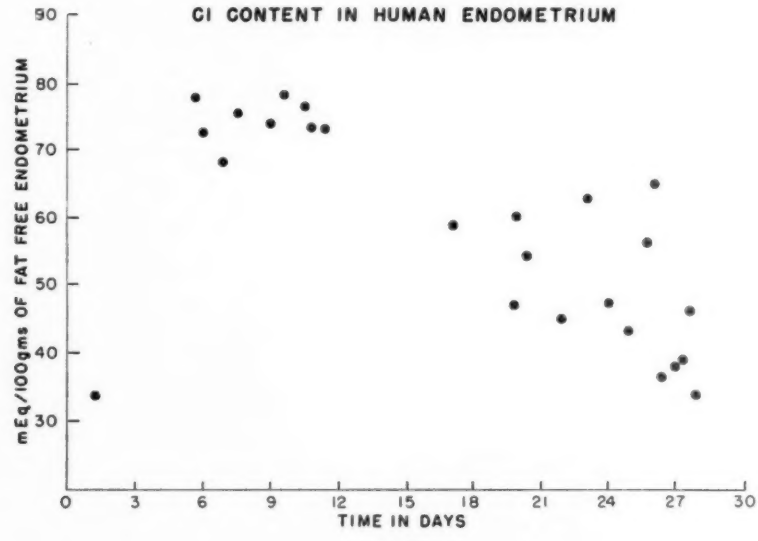

Fig. 4.

There is some evidence of a secondary increase in chloride concentration at days 23 to 26. Sodium values varied from 45.8 to 110.1 mEq. per 100 grams of fat-free tissue. Chloride values varied from 33.6 to 78.1 mEq. per 100 grams of fat-free tissue. These high values for the tissue electrolyte content are in keeping with the high values noted before in uterine tissue[8]; these values are in good accord with recent determinations on human endometrium,[9] though somewhat higher since they are expressed in terms of fat-free weight.

Fig. 5 demonstrates variation in the sodium to chloride ratio. Most of the values fall along the 1.2 line as would be expected. Some of the early and late specimens, however, show a considerably increased sodium to chloride ratio. This will be discussed later.

Comment

Interpretation of whole tissue data such as these is difficult. For one thing, different cell types are involved, though they have a common origin. Also, sodium and chloride can no longer be considered to be exclusively extracellular in distribution, and since specific information as to their distribution is not available, the identity and meaning of the sodium and chloride spaces must be considered obscure.

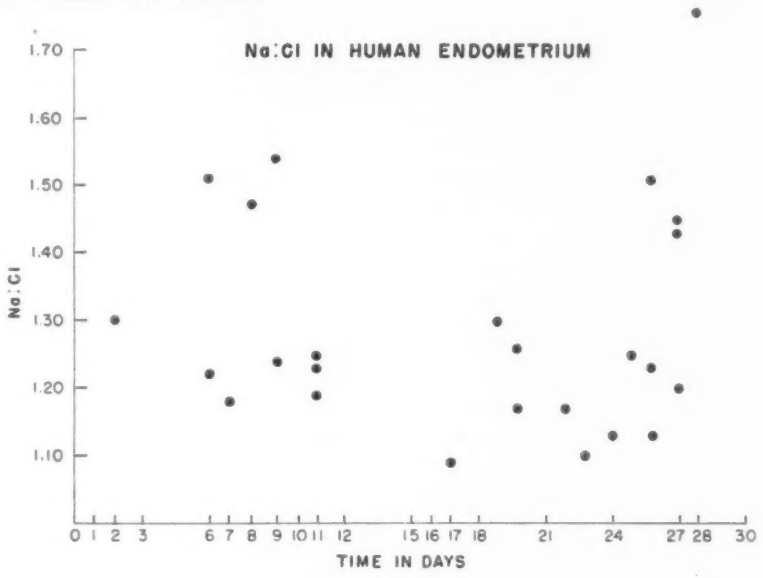

Fig. 5.

Although ions are known to cross the cell membranes at varying rates, a relatively constant composition is nevertheless maintained in the cells. According to Moore and associates,[10] about 20 per cent of the "active" sodium of the body is "nonextracellular," perhaps intracellular, though possibly some of this is skeletal. The chloride space is still considered an approximation of the extracellular volume,[10] although perhaps 5 per cent of the body chloride is intracellular. Certainly, intracellular sodium and chloride vary from tissue to tissue, and nothing is known of the distribution of these ions in the endometrium. The tentative conclusions in this paper are based on the assumption that a relatively constant intracellular composition is maintained, that 80 to 90 per cent of these ions are extracellular, and hence, since total tissue concentration of these ions is in direct proportion to the extracellular space, changes in the extracellular space are reflected by alterations in the total tissue sodium and chloride, the latter ion being the more accurate index.

The difference between the average concentration from day 6 to day 12 and that from 19 to 26 is about 22 mEq. per 100 grams. Considering the extracellular fluid to be about 15 per cent of the body weight, the difference in chloride values for the two periods would account for a change of about one-third, or about a 5 per cent change in extracellular fluid volume. In view of

the lack of statistical significance of the change in water content in these data, there is nothing to be gained by comparing the measured water change with that predicted from electrolyte changes.

Whereas McLennan and Koets[6] used relatively constant-sized single squares of tissue from each specimen for their water content determinations, it was necessary in this work to take scraps of tissue on occasion, and it is felt that this increase in surface area accounts for some of the low values in the present series, especially since a light blotting was a part of the procedure.

On the basis of per cent water and electrolyte studies, the conclusion can be drawn that there is no evidence to suggest that the histologist's secretory phase edema exists as a true edema. In fact, in view of the similar cyclical pattern obtained in three separate series, one of them statistically significant (and in view of the known hydrating effect of estrogen on tissues of the reproductive tract), the biological actuality seems to be that the water content is greater during the proliferative phase than it is during the secretory phase.

Thus it appears that there is a moderate, variable histological stromal edema during the proliferative phase, probably a true edema; and a more marked and constant intercellular swelling in the secretory phase, an atypical edema or a stromal spreading. In addition to the water and electrolyte data, there is evidence which suggests that the secretory phase "edema" is indeed an atypical occurrence, and one which may be functionally significant.

The reciprocal relationship between the secretory phase "edema" and the predecidual reaction has been noted histologically before. There is evidence suggestive of a functional relationship between the two processes. Van der Horst and Gillman[11] in the Elephantulus and other workers in other animals, have shown that implantation is preceded by, or associated with, a stromal "edema," which is followed in place by a decidual reaction, which reaction follows closely the progress of the "edema" toward the myometrium. In addition, Ober[17] informs me that on the basis of the study of 4 women followed throughout the secretory phase with 4 endometrial biopsies on each, he has made the tentative observation that the extent of the predecidual reaction is parallel to the extent of the "edema" or stromal spreading. Perhaps, then, the stromal spreading is a necessary precursor of the predecidual reaction, and the former supplies substances necessary for the dramatic increase in size of the stromal cells in becoming predecidual or decidual cells, either by supplying small molecules by diffusion, or larger compounds by phagocytosis. Intercellular glycogen granules have been noted in the spread stroma, and Sylven[12] has noted that decidual cells contain abundant ester-sulfuric acids, typically intercellular material, in their cytoplasm.

Another interesting relationship was noted by McKay[13] in his study of metachromasia in the endometrium throughout the menstrual cycle. He observed a reciprocal relationship between the stromal spreading and the intercellular metachromatic substance, a mucopolysaccharide. The latter was present before and after the spreading, but absent during it. Thus it seems that the intercellular material changes character during the spreading, perhaps undergoing depolymerization and/or the influx of additional substances. Histochemical and chemical studies show that the secretory phase of the cycle is accompanied by an increase in glycogen, glycoprotein, mucopolysaccharides, and lipids.[14] Perhaps these substances are involved in this change of character of intercellular substance. It is interesting to note that there are two biological instances, the sex-skin swelling in the monkey, and the erection of the cock's comb, in which there is good evidence that the swelling is due to the secretion of mucopolysaccharides into the intercellular spaces. This secretion is controlled by sex steroids. Against any explanation of stromal spreading in terms of increased intercellular

mucopolysaccharides is the hydrophilic character of those compounds, seemingly contradictory of the decrease in per cent water noted. However, perhaps depolymerization and the inclusion of glycogen, glycoprotein, and/or lipid result in a sufficient decrease in hydrophilia to make this explanation plausible. Since implantation occurs on this "edematous" stroma, the presence of the above-mentioned substances in that stroma would provide the developing ovum with the type of substances which (as endometrial gland secretion) apparently sustain the ovum in its approximately 3 day stay free in the uterine cavity. The possible functional importance of this stromal spreading, then, is related to the provision of a suitable implantation site for the developing ovum. If this new concept of its significance is correct, the occurrence of a satisfactory stromal spreading may be an important factor in successful gestation, and a factor to be considered in sterility problems.

With regard to the cyclical variation in the ratio of sodium to chloride (Fig. 5), the majority of the specimens align themselves approximately along the 1.2 line, roughly that of serum. However, most of the specimens of the last 2 days of the period show a considerable increase in that ratio. This most probably represents a loss of integrity of the cell membranes, as a precursor of menstrual necrosis, with intracellular potassium being replaced largely by sodium, resulting in a high sodium : chloride ratio.

In addition, several specimens in the early proliferative phase show high sodium : chloride ratios. This may be a reflection of a specific level of estrogenic activity. In their study of the response of the rat uterus to 0.1 μg of estradiol, Talbot and associates[15] noted that with the first influx of water and electrolytes, sodium initially increased to a greater extent than did the chloride. Similarly, Kalman[16] showed that in the rat after estradiol the uptake of I^{131} by the uterus was commensurate with its uptake of water; however, the uptake of Na^{22} was greater than could be accounted for by the increase in water content. Thus it seems that in the rat, early in the response to estrogen, some sodium is intracellular. Perhaps the high sodium : chloride ratio in the early proliferative phase of human endometrium is a reflection of this type of initial response to estrogen.

Further investigation into the secretory phase "edema" or stromal spreading is desirable. A larger, more complete series is needed, particularly in view of the lack of specimens from day 12 to day 16. Perhaps preoperative tracers could be employed, simplifying the procedure. Microdissection and subsequent direct determination of tissue compartments is the ideal approach to this problem, but unfortunately not an easy one. Further chemical and histochemical studies of the endometrium, in line with this new concept, may serve to clarify the problem.

Summary

Data are presented showing statistically significant cyclical variation of endometrial sodium, chloride, and potassium content. No significant cyclical variation in water content is noted. The histologically noted secretory phase stromal edema is considered in the light of these data, and speculation made as to its true nature.

I am deeply indebted to Professor Earl T. Engle, Dr. Gilbert J. Vosburgh, and Dr. Louise L. Phillips for their generous help and good counsel.

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EXPERIMENTAL METAPLASIA OF THE ENDOMETRIUM

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THIS paper is intended to show how an extensive and, sometimes, atypical metaplasia can be experimentally induced by a prolonged traumatic stimulation of the endometrium.

Procedure and Findings

The following experiment originated from a peculiar clinical case.

A woman, aged 62, was admitted to the clinic because of irregular vaginal bleeding. A total hysterectomy was performed. The uterine cavity contained a foreign body, which was diagnosed at the Botanical Institute as a spike of *avena barbata.* Complete recovery followed the operation.

Microscopically, the site of implantation of the barbs showed an intense inflammatory reaction, with large areas of epithelial metaplasia. A review of the literature on foreign bodies did not reveal any corresponding case. But an interesting and unsuspected similarity was traced in several experiments on the lingual mucosa of mice and rats.

Stahr,[1] Fibiger,[2] and Secher[3] reported hypertrophic and hyperplastic changes, which were variously interpreted as atypical epithelial proliferations or cancerous lesions after feeding mice and rats for a 3 to 4 month period with Danish oats or barley.

As the results of these experiments showed a definite similarity to the histologic changes found in our clinical case, it seemed logical to experiment with the same mechanical agents on the rat uterus.

Spikes of *avena barbata* or *"setaria glauca"* and Verticillata (varieties of Italian oats) were implanted by laparatomy in the right or left uterine horn, about 2 inches above the external os. The insertion was made in the direction opposite to uterine contractions.

The total number of animals was 35. Five uteri were submitted to vital staining with 2.5 per cent lithium carmine.

They were killed from the twentieth to the one hundred twentieth day following the operation. No complications were noticed during this interval.

In every case the regional lymph glands were microscopically examined.

The microscopic changes which follow the implantation of foreign bodies can be divided into two successive stages.

The first one corresponds to a simple metaplasia of the superficial and glandular epithelium, with all the histologic aspects of an inflammatory reaction. The second stage becomes so close to a neoplastic process as to render very difficult a differentiation from a real carcinoma.

The intensity and the extension reached by these changes vary from case to case; the chronologic succession is also different.

From the twentieth day on, the inflammatory reaction is evidenced by an infiltration, both in the stroma of the mucosa and in the connective tissue of the myometrium, of histiocytes and fibroblasts.

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Lympholeukocytes, plasma cells, mast cells, eosinophilic cells, and giant cells are predominant when metaplastic changes are accompanied or followed by a degeneration of the epithelial cells.

Fig. 1.

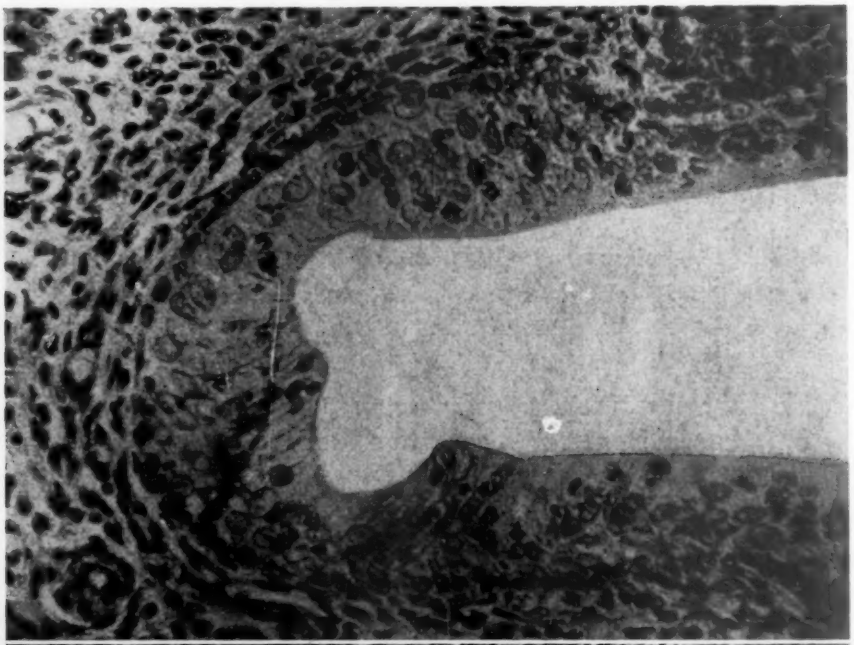

Fig. 2.

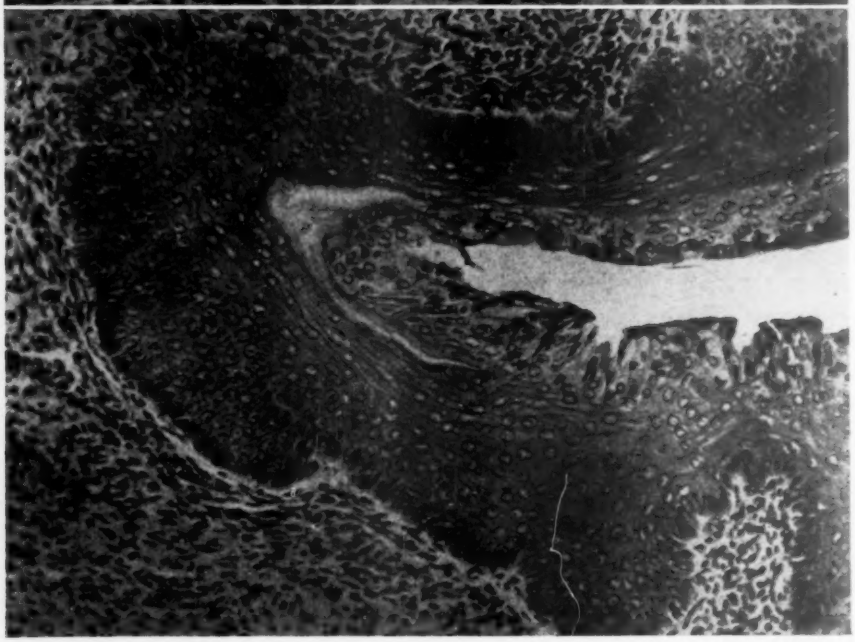

Fig. 1.—Early proliferative phase of basal cells. An uninterrupted layer of basal cells is evident between the columnar epithelium and the basement membrane (twenty-second day experiment).

Fig. 2.—The basal cells have already undergone a differentiation into squamous epithelium. The basement membrane is still intact; a tendency to form papillae is under way. The columnar epithelium is degenerating and partially cast off in the uterine cavity (thirty-fourth day).

Whatever may be their designation (intraepithelial, reserve, embryonic, etc.), the basal cells promptly react to the traumatic injury brought up by the foreign bodies.

While in normal conditions they seldom form a regular line under the columnar epithelium, after 3 to 4 weeks they accumulate in one or several layers of cells (Fig. 1).

Fig. 3.

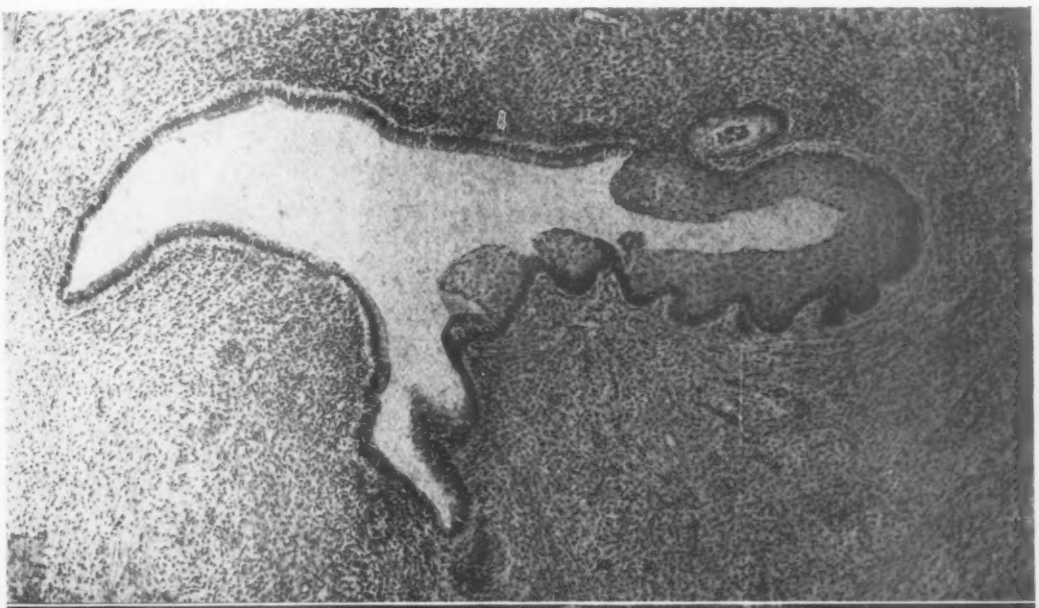

Fig. 4.

Fig. 3.—Isolated area of metaplasia. While most of the uterine cavity is lined by a single layer of cylindric cells, one segment shows definite stratified squamous epithelium (thirty-sixth day).

Fig. 4.—Section through both the uterine cornua. The left side appears normal. The right one, where the spikes were inserted, reveals extensive metaplastic changes (forty-fourth day).

At the beginning, the basal cells are lined up regularly, one next to the other. Numerous mitoses now become evident; most of them are normal.

Fig. 5.

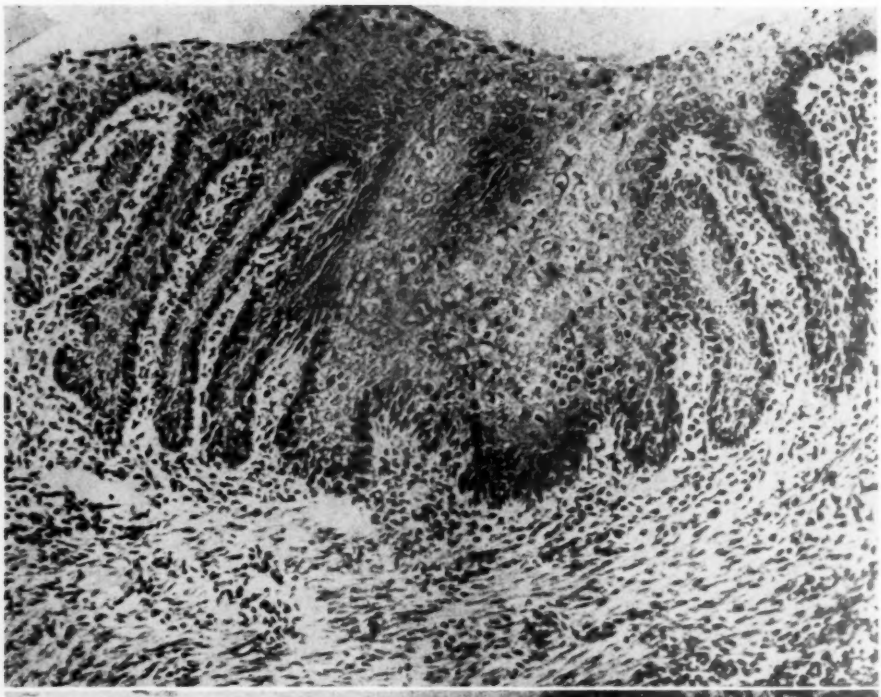

Fig. 6.

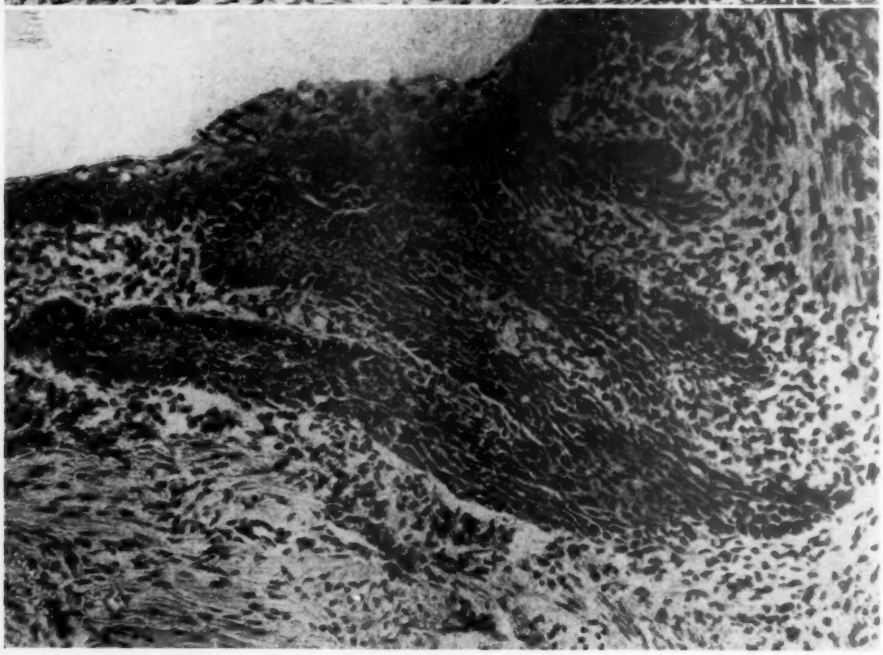

Fig. 5.—Advanced differentiation of the squamous epithelium. Basal cells line only the borders of the papillae (forty-sixth day).

Fig. 6.—Differentiation of the basal cells is generally missing. They form most of the invading papillae (forty-eighth day).

Fig. 7.

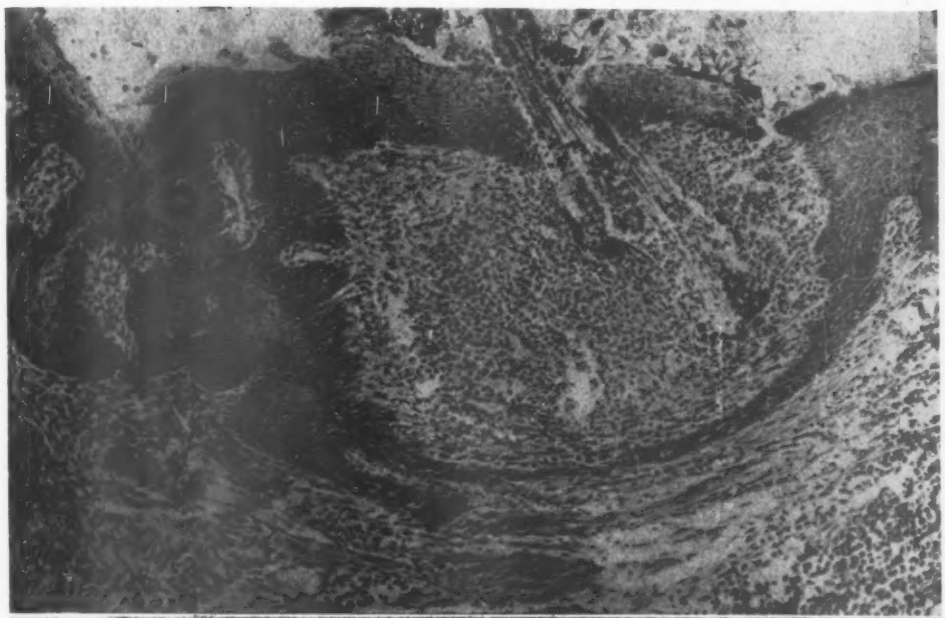

Fig. 8.

Fig. 7.—Crescentlike proliferation of the metaplastic epithelium around the implanted spike (fifty-second day).

Fig. 8.—The squamous epithelium has invaded the glands. Some appear cystic; others are transformed into solid strands. The limit between the endometrium and the muscular layers is partly lost (seventy-sixth day).

Contrasting with the proliferation of the basal cells are the degenerative changes affecting the cylindric cells which still line the endometrium. A vacuolization of the protoplasm becomes more and more evident, while chromatolysis and karyorrhexis of nuclei take place. As a final result, the cylindric cells are desquamated into the uterine cavity (Fig. 2).

The superficial epithelium is transformed into a transitional one through a gradual differentiation of the basal cells. It is formed by a few layers of cells, which do not have a definite orientation. In the deeper layer they still have an embryonic aspect: They become much larger and mostly polyhedral in the upper layers.

Fig. 9.—Advanced stage of epithelial infiltration into the uterine walls. Large islands of squamous epithelium are deeply embedded in the myometrium. Most of them show degenerative changes in the center (one hundred and eighth day).

The extension reached by the metaplastic process varies from one slide to another. While it affects, in some, the whole surface of the uterine cavity, it is limited in others to circumscribed areas.

A sudden change in the superficial epithelium is evident in Fig. 3. Patches of squamous epithelium are interposed between the cylindric cells.

Quite different are the microscopic aspects in Fig. 4.

While the right uterine cavity shows an extensive epidermization of the endometrium, the left one—serving as control—is lined by a normal, cylindric epithelium.

The regenerative process, which leads first to a transitional, later on to a squamous epithelium, affects in early stages only the superficial cells. It involves—in a progressive succession—the glands through a secondary invagination of the squamous cells.

The glands are either transformed into small cysts by the obliteration of the ducts, or changed into solid cords.

The transitional epithelium undergoes a further differentiation into a typical squamous, stratified epithelium.

The cells become larger, polyhedric: they are sharply delimited by a protoplasmic membrane, from which fibrillike ramifications are projected into intercellular spaces. A real stratum spinosum is thus formed.

From the deeper layers numerous papillae project into the stroma. Some, as in Fig. 5, show an orderly arrangement of the epithelial cells. Others, as in Fig. 6, are represented by immature cells.

Very impressive is the histologic picture in Fig. 7. The barbs of the spike, deeply implanted in the endometrium, are surrounded by crescentlike epithelial papillae, converging toward each other, so as to block them from the deeper tissues.

The tendency of the papillae to infiltrate not only the mucosa, but—later on—also the myometrium, along with the transformation of the glands into solid cords of cells, changes the microscopic picture from a simple epidermization to what seems to become a neoplastic process (Fig. 8).

Numerous and extensive strands of epithelial cells infiltrate the myometrium in Fig. 9.

While in some of them proliferative changes are still evident, in others degenerative changes become predominant. The center is often transformed into a cavity filled with cellular detritus, or, when cornification or hyalinization takes place, some "pearls" make their appearance.

No metastases were found in the regional lymph glands.

Comment

Microscopic findings demonstrate that a prolonged traumatic stimulation is capable of inducing an extensive and, sometimes, atypical epidermization of the endometrium.

The metaplastic changes originate from a proliferation and heteroplastic differentiation of the basal cells.

In a previous publication[4] on basal-cell carcinoma I have explained the reasons why a benign metaplasia cannot always be differentiated from a malignant one, and I have, consequently, reviewed many cases previously described as squamous carcinoma of the endometrium.

Experimental investigations, such as the present one, have even complicated the differential diagnosis. While in morbid conditions the metaplastic changes may be considered benign as long as the mucosa only is involved, in experimental conditions some doubts persist even when the epithelial cells show an aggressive attitude.

The ambiguity of the histologic findings is evident in similar experiments on the tongue: it has already been mentioned that these were variously interpreted as atypical epithelial proliferations or carcinomas.

Experiments with different techniques on many other organs (stomach, bladder, peritoneum) similarly have failed to yield definite conclusions.

As far as the uterus is concerned, it seems that trauma alone is unable to induce real carcinoma. This has sometimes developed when to a traumatic lesion of the cervix is added an epithelial stimulation with estrogens.[5]

The diagnosis of carcinoma is esentially based on cellular atypia, invasiveness, metastasis. As the last was consistently absent, the diagnosis has to resort to the aspect and to the location of the epithelial cell. The degree of cellular atypicality is not decisive for a diagnosis of cancer. Whenever the basal cells undergo an intense proliferation, they may show a large number of atypical mitoses and irregular changes of nuclei and protoplasm. They have been noticed in many other organs in the course of hyperplastic or anaplastic processes, without reaching the final stage of real carcinoma.

The size, the shape, and the staining of the nuclei are also indecisive findings; in every regenerative process there is a certain degree of polymorphism due to a different degree of differentiation of the epithelial cells.

Even the appearance of intra- or paranuclear eosinophil granules, which has sometimes been considered a significant finding in experimental tumors, does not seem specific for neoplastic cells. The same granules have been found—in conjunction with a hyaline or colloid degeneration of the protoplasm—in the epidermoid lining of many other organs.

Similar objections can be raised in respect to the hyaline or horn "pearls" which were found in some of our slides. They are not specific for carcinoma, as they may also occur in atypical inflammatory proliferations.

Of greater importance is the invasive power of the metaplastic epithelium.

The invagination of the squamous epithelium into the glands does not really correspond to an invasive process. As the inflammatory changes, which are responsible for the metaplasia, usually start from the surface of the endometrium, it is not surprising that they extend—as a natural defense—to the more deeply situated glands. The same topographical sequence has been noticed in morbid conditions. The undermining and, later on, the substitution of cylindric cells has not been considered as really heterotopic as long as the basement membrane is intact. But not even on this point has a complete agreement been reached. Some authors believe that the perforation or dissolution of the basement membrane is not a pathognomonic sign of cancer, because it can be present in hyperplastic changes of the glands, while it may be absent in real carcinomas.

Three different conditions could have contributed, in our experiments, to the infiltration of the epithelial cells in the myometrium:

1. The expansion of the glands following the transformation into solid strands of cells and a consequent compression of the basement membrane. This could lead to a break-through of the membrane, as happens in cysts or myomas, according to Meyer.

2. The inflammatory changes could be responsible for the heterotopia, as heterotopic glands have frequently been found in so-called adenomyometritis.

3. A traumatic injury by foreign bodies, by a direct displacement of the epithelial cells.

Conclusions

1. The insertion of spikes of *avena barbata* or *setaria* in the uterine cavity of white rats is followed in a short time by proliferation of the stromal tissue of the mucosa and myometrium; atrophy of the glands; degeneration and desquamation of the superficial epithelium, accompanied by basal-cell hyperplasia.

2. The squamous, stratified epithelium originates from a hetero-plastic differentiation of the basal cells. It signifies a defensive process.

3. Metaplastic changes affect initially the surface of the endometrium. They extend, in succession, to the glands through a secondary invagination of the superficial epithelium. The glands are either transformed into solid cords, or into small retention cysts.

4. Neoplastic-appearing aspects can be simulated by cellular anaplasia and by invasiveness of the metaplastic epithelium. A diagnosis of carcinoma can be ruled out by the lack of a real destructive power and by the absence of metastasis.

5. The results of this experimental investigation prove that a distinction should be maintained between an atypical cellular proliferation, which may occur in the course of a metaplastic process, and real carcinoma.

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CONCURRENT AND INTERRELATED STROMAL ENDOMETRIOSIS (STROMATOSIS; STROMAL SARCOMA) AND UTERINE ADENOMYOSIS

Illustrative Case

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ADENOMYOSIS of the uterus is so common[1] that its occasional presence with the infrequent entity, stromal endometriosis, should not be surprising.

In previous studies[2, 3, 4] one of us (W. C. H.) has expressed the opinion that uterine adenomyosis and stromal growths of the uterus have much in common and indeed may be regarded as variants of a single process. Each tends to extend locally in the same manner. Yet the first shows little evidence of neoplastic behavior, while the other acts as a neoplasm but in a very special way.

While there have always been differences of opinion as to whether stromal endometriosis is a good term and as to whether it is really sarcomatous, there has been near unanimity that origin is from the endometrial stromal cell. This view was first challenged by Pedowitz, Felmus, and Grayzel,[5] who claim to have demonstrated that such tumors arise from pericytes and thus are hemangiopericytomas, a concept that we have not been able to accept. The case to be described seems to provide the proof of the stromal-cell theory of origin.

Mrs. C. T., a 45-year-old married woman, was seen by Drs. William Wagner and W. Lyle van Buskirk of Everett, Washington, with the complaint of abnormal vaginal bleeding. The menstrual periods occurred at 3 to 4 week intervals, lasted 7 or more days and, for 6 months, had been accompanied by clots, cramps, soreness over the lower abdomen, and low backache. Prior to the first office visit the menstrual flow had been continuous for 3 weeks with the exception of a 4 day free period. A similar episode, occurring 3 years previously, had led to a dilatation and curettage, the pathologic report of Dr. Emmanuel Bitar at that time being: "benign endocervical polyp; chronic cervicitis; early secretory endometrium with occasional cystic endometrial gland—benign."

Physical examination now showed a moderately enlarged, hard, and somewhat nodular uterus, and an enlarged, firm, tender right ovary. The only laboratory finding of importance was a hemoglobin of 10.7 Gm. and a hematocrit of 36 per cent.

Pathologic Study (G-57-547).—

Gross description: The uterus, oviducts, and ovaries weighed 150 grams. The external contour of the uterus was normal and it had a maximum dimension of 8 cm. The endometrium was 1 mm. or less in thickness. A somewhat ill-defined mass about 4 cm. in diameter projected into the cavum uteri; it was moderately firm, had a whorled appearance, and seemed somewhat friable. Several very discrete spherical yellowish-gray tumors, the largest 5 mm. in size, lay in the myometrium.

The significant gross features of the previously fixed and sectioned uterus are depicted in Fig. 1, *A* and *B*. Section *A* exhibited two intramural whitish bodies, side by side, measuring 5 and 7 mm. Between these and the uterine cavity was a less well-outlined yellowish area which on additional sectioning, at intervals of 3 mm., proved to be part of a coarse muscle tissue containing a tiny cyst—features suggestive of adenomyosis. A tiny segment of uterine cavity could be identified nearby. Along a border which gave evidence of being a cut made before fixation and 1.5 cm. from the uterine cavity were three small rounded protrusions and a polyp 9 mm. long, 1 mm. in thickness at the base, and 4 mm. across the free end. These latter features were highly suggestive of the intravascular extensions of stromal endometriosis.

Segment *B* contained a bit of uterine cavity lined by endometrium and consisted mainly of coarse myometrium, save for the outermost 5 mm. Within the muscle tissue, but close to the endometrium, was a mass of tissue, softer than that elsewhere, somewhat yellowish in color. Extending outward from near the uterine cavity was what appeared to be a previously severed polypoid body. New sections of this body showed a soft, white tissue which changed rather abruptly to the coarse adenomyotic lesion farther from the endometrium.

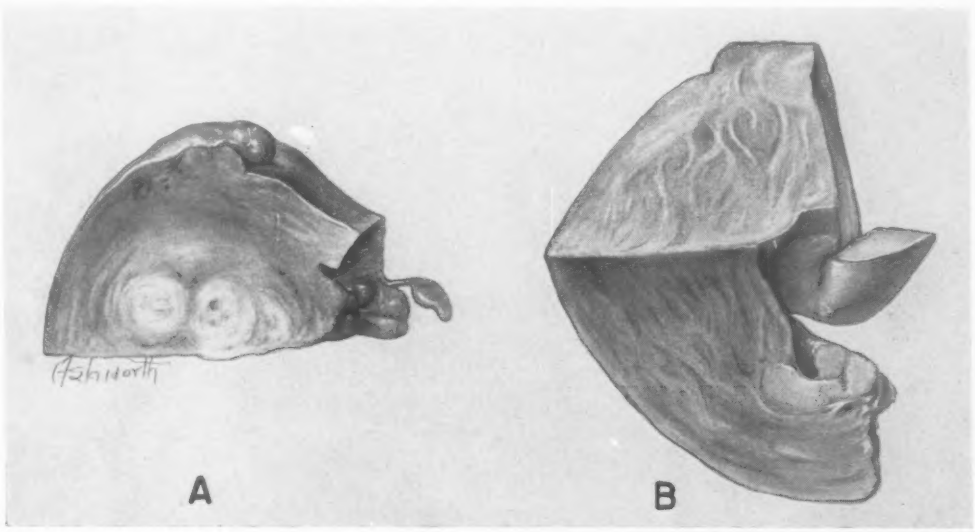

Fig. 1.—Natural size half tone drawings of the significant parts of the uterus (G-57-547).

A, Along the smooth-cut surface are two leiomyomas and, nearby, a streak of white tissue which proved microscopically to be adenomyosis; the cavum uteri is a small curved slit close to the focus of adenomyosis. The right border is a surface made by sectioning before fixation and illustrates convincingly the rounded protrusions and polyp formation so likely to occur in stromal endometriosis.

B, The evident polyp is submucous adenomyosis; the three white bodies below are likewise adenomyosis, the seat of considerable hyaline degeneration. The coarseness of much of the myometrium is attributable to hyperplasia of smooth muscle in conjunction with adenomyosis.

Microscopic description: Out of the diverse histopathologic picture exhibited by many sections of the uterus the following points are significant: (1) The endometrium, in the proliferative phase, was unchanged along one side of the cavum while on the other there were a meeting and intermingling of normal endometrial stroma and of cells that were larger, darker staining, and clearly neoplastic; in Wilder reticulum stains both the normal and the neoplastic cells were surrounded by fibrils. (2) There was widespread heterotopia of endometrium into myometrium; the latter was hyperplastic, as is characteristic of adenomyosis. (3) In juxtaposition with the endometrium were small vascular channels and herniation of stroma into these, as occur regularly along the advancing frontier of adenomyosis. (4) The polyp and multiridged body (Fig. 1, *B*) represented foci of polypoid

adenomyosis. (5) The whitish intramural bodies (Fig. 1, *A*) were leiomyomas. (6) Not appreciated macroscopically but evident enough in large sections of uterine wall was a focus impressively unlike the above enumerated entites and deserving of critical evaluation.

This special area, in direct continuity with normal stroma and endometrial glands, consisted in myriads of cells with nuclei distinctly larger and more chromatic than the nearby normal stromal cells (Figs. 2, 3, 4). The nuclear chromatin was evenly distributed; mitoses were not observed. Although distinctly different from the normal stromal cells, these larger cells were as uniform among themselves as the nonneoplastic ones. The vascular component of the neoplastic tissue was more prominent than in the adenomyotic endometrium, in part owing to the thickness of the walls of some vessels and because of the huge lumina of many of the thin-walled vessels (Fig. 3). All of those with thick walls were blood vessels but only those of the thin-walled channels containing erythrocytes were certainly identified as blood vascular channels.

Fig. 2.

Fig. 3.

Fig. 2.—Photomicrograph of section of uterine wall, including endometrium (bottom) and perimetrium (top). The pale and irregularly outlined areas toward the base are foci of adenomyosis where hyalinization has occurred. In the mid-zone are endometrial glands, vessels, and tumor. The peripheral portion is unchanged. Details of the blocked-off area are better appreciated in Figs. 3-5 inclusive. (×14; reduced 2/7.)

Fig. 3.—Photomicrograph of the marked area of Fig. 2. At the lower right corner is an endometrial gland containing blood; the adjacent stroma here and almost everywhere else in the field is neoplastic and in it are many huge thin-walled vascular channels together with blood vessels that have definite walls. The lower left corner consists of endometrial glands with normal stroma. The intravascular polyp pictured in Fig. 4 is near the right upper corner. (×40; reduced 2/7.)

Three of the thin-walled vessels within the tumor are of paramount interest. Fig. 4 depicts an intravascular polyp, the free end of which consisted of cells indistinguishable from normal endometrial stroma but at the base changing to a perceptibly larger cell, directly continuous with the cells composing the stromal tumor adjoining the vessel. The polyp, like the blood vessel into which it extended, was overlaid by endothelium. Here, better than anywhere else, is microscopic proof not only of the coexistence of adenomyosis and stromal endometriosis but also the inception of blood vessel extension of stromal endometriosis. Continuous with the neoplasm on every side of another thin-walled vessel (Fig. 5) and herniating far into its lumen was an intravascular extension of spindle-shaped tumor cells. Again, as elsewhere, fine reticulum enveloped the individual cells. Last, the small polyp pictured in the gross drawing (Fig. 1, *A*), proved to be stromal tumor protruding from a vessel cut across when the tissue was fresh.

Thus, at three points within this tumor and its concomitant adenomyosis was exemplified the well-known tendency of adenomyosis and stromal endometriosis to push along vessels

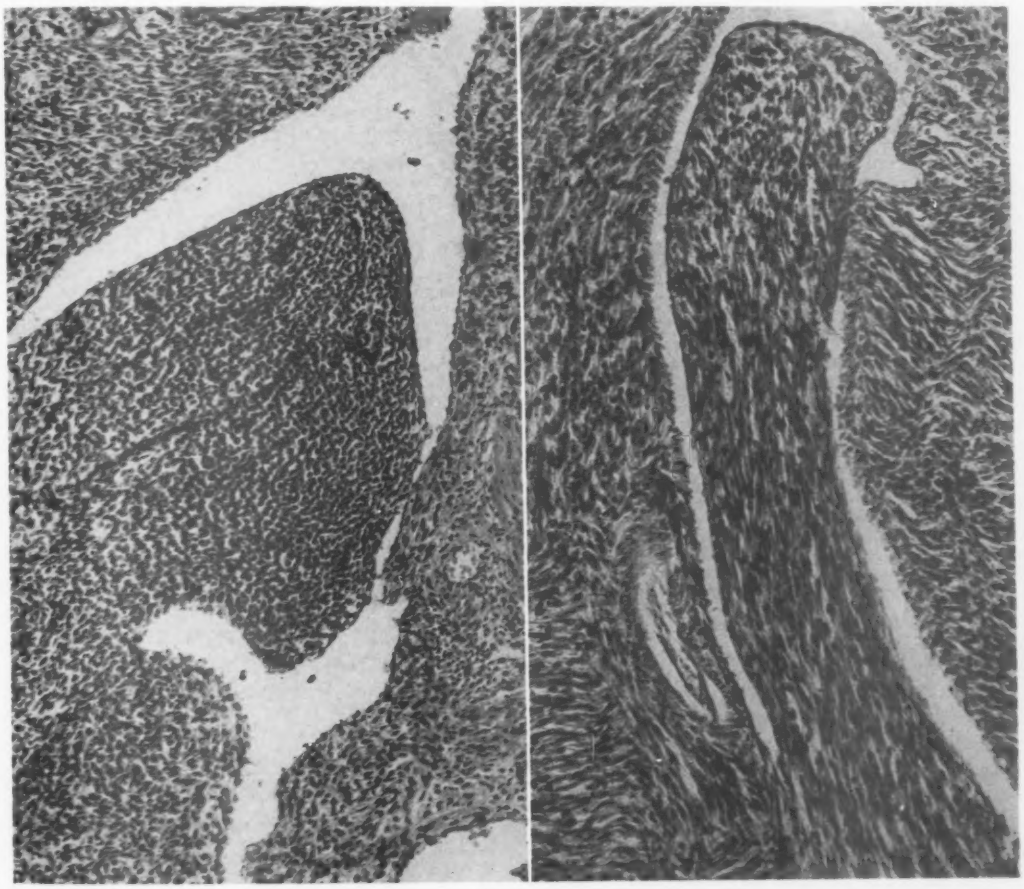

Fig. 4. Fig. 5.

Fig. 4.—Details of the intravascular polyp located near the upper right margin of Fig. 3. The cells at and near the free end of the polyp are indistinguishable from normal endometrial stroma elsewhere but toward the base become perceptibly larger and merge imperceptibly with the tumor mass on every side of the vessel. Endothelium covers the polyp as well as the vessel. Erythrocytes at the upper end prove that this is a blood vessel channel. On the extreme right is a small amount of normal myometrium. (×200; reduced ⅓.)

Fig. 5.—An entirely neoplastic but still endothelium-covered polyp in a vessel of uncertain nature. Part of the point of origin of the polyp is seen along the left base, joining with tumor cells outside; otherwise the polyp is entirely free. (×400; reduced ⅓.)

and to herniate into their lumina. Since one of these appeared to be a mixture of original endometrial stroma and neoplastic stromal cells, it served as a connecting link between adenomyosis and stromal endometriosis.

In all sections containing endometrium, normal endometrial stroma, or stromal tumor, Wilder reticulum-stained preparations showed basketlike arrangement of fibrils about individual cells. There was no concentration of reticulum or cells immediately outside any of the vessels. Neither the reticulum stains nor the van Gieson preparations demonstrated the "occult" vessels said to occur in hemangiopericytoma.[5]

Of interest and even of possible importance in tracing the transition of endometrial stroma to stromal new growth in this instance was the observation of scattered phagocytes containing blood pigment in both types of tissue. It is not uncommon to find such pigment in entirely normal endometrial stroma, particularly if bleeding has occurred.

Comment

This case of intramural and also submucous polypoid uterine adenomyosis exhibited a focus, not over 2 cm. in extent, which met the histologic criteria for stromal endometriosis. Of the greatest interest is the fact that in some areas adenomyosis and stromal neoplasia not only were present together but exhibited direct transition from adenomyotic stroma to neoplastic stroma, while in other situations misplaced glands with normal stroma lay buried in stromal new growth, untouched. Furthermore, both in gross and in microscopic form, intravascular extension of adenomyosis and stromal endometriosis was demonstrable.

It is common knowledge that at the advancing margins adenomyosis spreads by spearing out of endometrial stromal cells alongside thin-walled vessels, the glands coming along later, and that often enough one may observe stromal herniation into vessels, forming polyps. If perchance the section is so cut that the connection of a polyp is not shown, a perfect imitation of stromal endometriosis is produced; or if the connection is present but the polyp lacks glands the appearance is indistinguishable from that of stromal endometriosis. Individually the cells of the two conditions are quite alike.

In a previous paper[4] one of us (W. C. H.) said, in part: "we have found no reason to alter the earlier expressed concept that stromal endometriosis is a peculiar neoplastic variant of the very common nonneoplastic entity known as adenomyosis. . . . Since endometrial glands and stroma are variants of the same parent cell, is it not possible that, given the proper stimulus, whatever this may be, both glands and stroma may proliferate in one uterus and stroma alone do so in another? The proportions of the two cell elements may vary. A number of writers as well as ourselves have observed typical cases of stromal endometriosis containing occasional glanduliform structures, a finding that bridges the gap between pure adenomyosis on the one hand and pure stromal endometriosis on the other."

This is where the matter stood with us in 1956. The present study leads us to believe that not only can adenomyosis and stromal endometriosis be concurrent but comingle and that a direct transition from the stromal cells of adenomyosis, normal in every respect save for heterotopia, to neoplasm can take place. The striking tendency of both conditions to push into vessels is convincingly demonstrated in this case.

It is not our intent to imply that adenomyosis and stromal endometriosis bear a cause-and-effect relationship to each other. In fact this is the first instance in which we have found them present together to more than a minor degree. What we do mean is that it is reasonable to believe that these two

conditions may have a common parent cell embryologically, that one stimulus may lead to adenomyosis, another to stromal endometriosis, and that both are prone to push along and into vascular channels.

In our opinion the case offers convincing proof that the peculiarly behaving tumor, so-called stromal endometriosis, actually originates from the stromal cells of endometrium and not from real or fancied pericytes.

The clinical features of the case are quite in keeping with those of adenomyosis of the uterus.

Summary

1. In a case clinically and pathologically typical of uterine adenomyosis it has been shown that an area of heterotopic endometrium has become, in part, transformed into equally typical stromal endometriosis.

2. There is histologic evidence that the cell of origin of stromal endometriosis is the interglandular supportive cell of endometrium.

3. The case offers additional evidence of the concept that adenomyosis and stromal endometriosis may stem from an obscure abnormality of growth and maturation of endometrium.

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THE USE OF NEWER PROGESTINS IN THE TREATMENT OF ENDOMETRIOSIS*

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ENDOMETRIOSIS may be defined as the presence of functioning endometrial tissue outside of its normal situation but usually confined to the pelvis in the region of the ovaries, uterosacral ligaments, and uterovesical peritoneum. It is characterized symptomatically by progressive, increasingly severe pelvic pain associated with or occurring just prior to menstruation. The crippling characteristics of this malady, occurring during the reproductive period of women, prevent fulfillment of marital potential since sexual intercourse is often painful and childbearing frequently impossible. Definitive treatment has all too often been surgical in the way of hysterectomy and castration with development of subsequent neuroses and occasional psychoses.

In 1953, Meigs[1] suggested a method of prophylaxis against endometriosis —early marriage and early childbearing. He even exhorted parents to subsidize their sons and daughters so that this might be financially feasible. Meigs stated at that time: "It is the author's belief that avoidance of endometriosis through early marriage and frequent childbearing is the most important method of prophylaxis."

However, in many patients with this disease conception is not always possible either because of unknown factors producing infertility or because marriage is not contemplated. As a substitute the author has induced a state of "pseudopregnancy" in 12 patients by combining large doses of estrogenic substances and 2 of the newer progestins in a graduated scale for periods of time up to 7 months. It is postulated that the improvement noted in endometriosis during and after pregnancy is due to the production of a decidua in these areas as a result of increasing levels of estrogen and progesterone. As the pregnancy progresses, areas of necrosis occur in this decidua and, accordingly, in the areas of endometriosis. This finding has been observed in patients who have ovarian endometriosis proved by resection at the time of cesarean section (Fig. 1).

Material and Method

All patients treated during this study were seen in the outpatient department of the Free Hospital for Women or in my office. Selection of patients was made on the basis of clinical criteria such as: (1) acquired, progressive

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dysmenorrhea; (2) cul-de-sac and uterosacral nodularity and tenderness; (3) fixed retroversion of the uterus; (4) tender adnexal masses. In most patients at least 3 of these 4 criteria were present. One patient was treated because of extensive vaginal endometriosis proved by histologic examination. The ages of the patients varied between 21 and 34. Ten were married and 6 offered the additional complaint of infertility. All had previously been treated by combinations of analgesic drugs and 6 had had periods of induced anovulation by estrogenic substances. Two had noted temporary improvement during prior androgen therapy.

An endometrial biopsy was obtained during the secretory phase (between days 12 and 23) of the menstrual cycle to serve as a control. All 12 patients showed evidence of ovulation as determined by these biopsies and no abnormalities of endometrial growth were apparent.

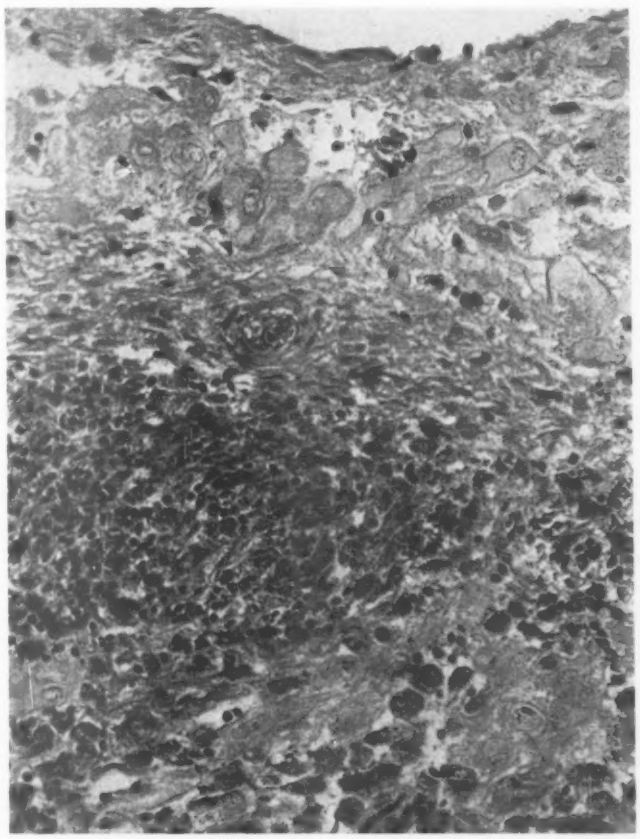

Fig. 1.—(S-BLI-57-702.) Shows an area of endometriosis of the ovary removed at the time of cesarean section. Under the surface epithelium ectopic decidual cells are evident, some of which are necrotic. In the central portion of the photograph is an area which contains many hemosiderin-laden macrophages, blood pigment, degenerated endometrial stromal cells, and lymphocytes. This picture is frequently seen in the wall of "burnt-out" endometrial cysts. (×40; reduced ¼.)

Two progestins were utilized to bring about the desired decidual effect. They are: (1) 17-alpha-hydroxyprogesterone caproate (Delalutin) and 17-alpha-ethynyl-17-hydroxy-5 (10)-estren-3-one (Enovid). The structural formulas are given in Fig. 2. Both of these substances have been shown in both animal and human experiments to exert a marked progestational effect upon the endometrium and both are well tolerated.

Pharmacology

1. Delalutin (17-alpha-hydroxyprogesterone caproate).—In a recent report by Reifenstein[2] a review of animal studies by Junkmann[3] and Kessler and Borman[4] was given. These indicated that Delalutin (in appropriate doses) has a progestational action that: (1) appears just as promptly, is at least twice as marked, and is 2 to 4 times more prolonged than that of free progesterone; and (2) is at least 30 times more marked, and at least 5 times more prolonged than that of free 17-alpha-hydroxyprogesterone.

Animal experimentation: A very marked and prolonged progestational action on the endometrium of rabbits has been demonstrated by Junkmann[3] and by Kessler and Borman.[4] The corpus luteum effect of 17-alpha-hydroxyprogesterone caproate has been confirmed by showing the presence of increased glycogen storage in the uterine mucosa and of greatly increased alkaline phosphatase activity in the epithelium, particularly in the submucosa of the fine mucosal folds. Further studies[4] indicate that 17-alpha-hydroxyprogesterone caproate has no androgenic actions in rats. In humans, Boschann[5] found that the caproate ester has an action that persists for longer than 8 days and indicated that maximal secretory transformation was obtained following a single injection of 250 mg. or following 2 injections of 125 mg. each, when the endometrium of castrated women was first primed with estradiol benzoate. Cohen and his associates[6] found that 17-alpha-hydroxyprogesterone caproate was well tolerated, even in large doses, and that undesirable effects were minimal. Tyler[7] reported that the preparation could be given in substantial therapeutic doses without concern about local reactions.

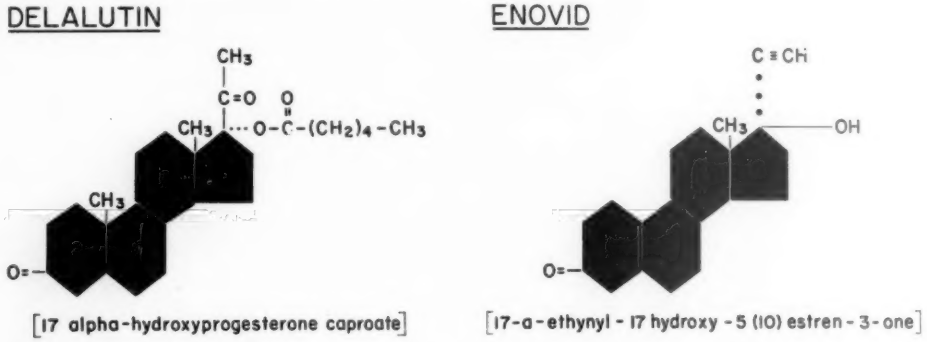

Fig. 2.—Structural formulas of the two progestins utilized in this study, Delalutin and Enovid. It should be noted that Enovid is a combination of norethynodrel (drawn above) and 1.5 per cent ethynyl estradiol 3-methyl ether.

Metabolism: The available evidence suggests that 17-alpha-hydroxyprogesterone caproate follows a different pathway of metabolism than does either 17-alpha-hydroxyprogesterone or free progesterone since the urinary metabolites following the injection of each of these compounds vary considerably. Thus free progesterone usually results in an increase in the urinary excretion of pregnanediol[8, 9]; 17-alpha-hydroxyprogesterone usually causes a decrease in pregnanediol excretion and a rise in the excretion of pregnanetriol and neutral 17-ketosteroids.[10, 11] The caproate ester similarly produces a diminution in pregnanediol excretion but only occasionally causes an increase in pregnanetriol excretion and does not cause an elevation in neutral 17-ketosteroids.[6, 10, 11] The mechanism for the prolonged progestational action of 17-alpha-hydroxyprogesterone caproate is not clear. It may be that the esterified steroid is transported intact to the tissues where it exerts its biologic activity, and there is slowly metabolized as it induces its action.

2. Norethynodrel (17-alpha-ethynyl-17-hydroxy-5(10)estren-3-one).—Norethynodrel is a new, synthetic chemical substance of the steroid class of drugs. It has been combined with not less than 1 per cent and not more than 2 per cent of ethynyl estradiol-3 methyl ether and studied clinically as SC-4642.*

By Clauberg assay (systemic administration of norethynodrel alone in estrogen-primed rabbits) this preparation was demonstrated to have a potent progesterone-like activity orally of the magnitude of parenterally administered progesterone. Animal experiments have shown that synthesis of gonadotrophins by the anterior pituitary is inhibited by adequate dosage. No androgenic potency was demonstated in castrated male rats by ventral prostate assay. Norethynodrel did not produce cortisone-like effects as judged by eosinophil counts in adrenalectomized mice. In diuretic assays, excretion of water and sodium was neither decreased nor increased by administration of the compound.

The most frequently encountered side action incidental to therapy is nausea, rarely vomiting. Occasionally breast engorgement and nipple pigmentation are seen. The drug, in common with most steroid substances, has a low order of toxicity.

In humans it has been possible to produce a secretory endometrium (with doses of 10 mg. daily) which is indistinguishable from that which occurs normally. Studies by Rock, Garcia, and Pincus[12] supply strong circumstantial evidence that ovulation may be inhibited in the usual dosage. This is based on studies of basal temperature curves, cervical and vaginal smears, pregnanediol excretion, and endometrial biopsies. Pincus[13] and Kupperman[14] report a sharp reduction in gonadotrophic excretion in the human during administration of Enovid while Heller[15] reports an altered but not a completely suppressed excretion.

The metabolism of this preparation, its site of action, and excretory metabolites are not known.

Therapeutic Programs

Several therapeutic schemes evolved as the study progressed. The first utilized was:

I. (a) Diethylstilbestrol (5.0 mg.) or Estinyl (0.05 mg.) given orally daily for one week and the dose increased 5.0 mg. (or 0.05 of Estinyl) each week. Thus at the end of 12 weeks a daily dose of 60.0 mg. (or 0.60 mg. Estinyl) was being taken.

(b) 17-alpha-hydroxyprogesterone caproate (Delalutin) was given by intramuscular injection beginning with 0.5 c.c. (62.5 mg.) weekly for 2 weeks. This was increased to 1.0 c.c. (125 mg.) during weeks 3 and 4; 1.5 c.c. (187.5 mg.) during weeks 5 and 6; 2 c.c. (250 mg.) during weeks 7 and 8; the dosage was then raised to 3 c.c. (375 mg.) during weeks 9 and 10, and 4 c.c. (500 mg.) during weeks 11 and 12.

A variation of the estrogen in this plan was:

II. (a) Estradiol valerate (Delestrogen) was given by intramuscular injection beginning with 1 c.c. (10 mg.) weekly for 2 weeks. This was increased by 0.5 c.c. every 2 weeks so that at the end of 12 weeks 3.5 c.c. (35 mg.) was being administered.

*Proprietary name is Enovid (norethynodrel with 1.5 per cent ethynyl estradiol 3-methyl ether) (Searle).

(b) 17-alpha-hydroxyprogesterone caproate (Delalutin) was administered as outlined in I (b).

Plans III and IV utilized Enovid instead of Delalutin.

III. (a) Diethylstilbestrol (5.0 mg.) or Estinyl (0.05 mg.) was given as outlined in I (a).

(b) Enovid (17-alpha-ethynyl-17-hydroxy-5(10)-estren-3-one with 1.5 per cent ethynyl estradiol 3-methyl ether) was given orally as follows: 10 mg. daily (1 tablet) for 2 weeks with increases every 2 weeks up to a total of 40 mg. The latter amount was the continuing daily dose.

IV. (a) No estrogenic substance given.

(b) Enovid was given as outline in III (b).

TABLE I. SUMMARY OF PLANS OF THERAPY

NAME	AGE	ESTROGEN	PROGESTIN	DURATION	REMARKS
Plan I.—					
1. J. A. (FHW-63005)	28	Diethylstilbestrol	Delalutin	2½ months	Therapy stopped because of pain
2. G. S. (FHW-63528)	34	Diethylstilbestrol	Delalutin	3 months	Improved*
3. L. P. (FHW-63336)	31	Diethylstilbestrol	Delalutin	3 months	Improved
4. L. B. (FHW-64665)	21	Diethylstilbestrol	Delalutin	4 months	Improved
5. A. A. (FHW-59387)	33	Diethylstilbestrol	Delalutin	4 months	Curettage for bleeding
Plan II.—					
6. M. H. (FHW-64852)	32	Delestrogen	Delalutin	4 months	Improved
Plan III.—					
7. P. S. (FHW-65046)	33	Estinyl	Enovid	3 months	Improved
8. R. H. (FHW-60159)	31	Estinyl	Enovid	3 months	Improved
9. R. L. (FHW-P.P.)	30	Estinyl	Enovid	4 months	Improved
Plan IV.—					
10. I. D. (FHW-65843)	29	--	Enovid	4 months	Now under treatment
11. E. J. (FHW-65243)	31	--	Enovid	7 months	Now under treatment
Combination.—					
12. D. D. (FHW-60779)	24	Diethylstilbestrol	Delalutin and (later Enovid alone)	4 months	Laparotomy showed decidua in endometriosis

*Improved refers to period of pseudopregnancy only.

The Analyses

Plan I.—Five patients were treated with Plan I (Table I). Two of these completed 3 months and 2 completed 4 months of therapy.

One patient (No. 1, J. A.) complained so severely of abdominal (uterine) crampy pain at 2½ months that medication was discontinued. (She described the pain as being like an abortion and following cessation of medication

"aborted" a large decidual cast.) All 5 of the patients who became "pseudopregnant" noted weight gain (as evidenced by edema and abdominal bloating), breast swelling, darkening of the nipples and areola, temporary nausea, and amenorrhea. Pelvic examination revealed softening and blue discoloration of the cervix and symmetrical, globular enlargement of the uterus with softening. During the third and fourth months of treatment changes in the characteristics of the posterior cul-de-sac and uterosacral nodules were evident. Masses and nodules softened or disappeared and fixed retroversions of the uterus seemed more mobile.

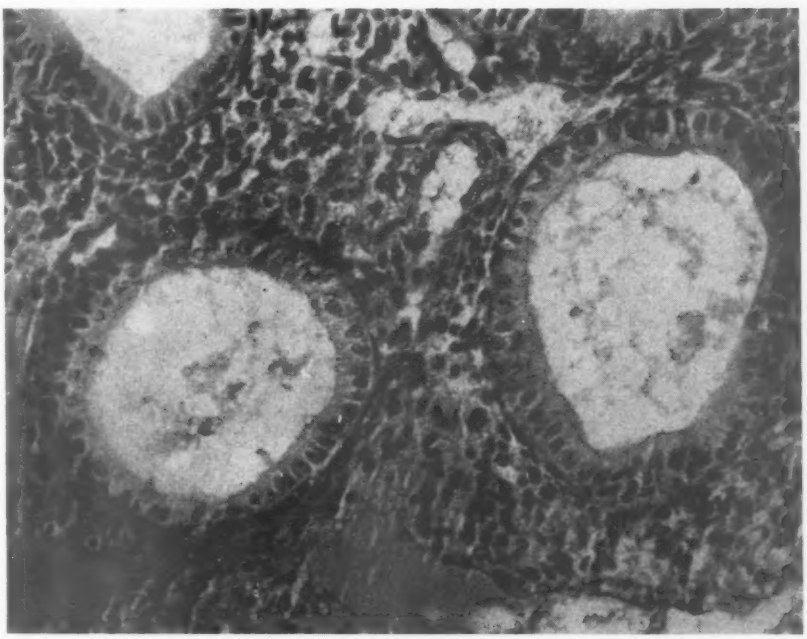

Fig. 3.—(FHW-S-56-1574, Patient No. 3.) High-power view of an endometrial biopsy taken during the control period showing normal secretory phase of about the twenty-second or twenty-third day of the cycle. (×200; reduced ¼.)

Patient No. 3 (L. P.) progressed favorably during a 12 week pseudopregnancy, noting only slight uterine pain and minimal irregular spotting. The striking changes brought about in the endometrium are illustrated in Figs. 3, 4, 5, 6, and 7. Fig. 3 illustrates an endometrial biopsy obtained during the control period termed 23 day secretory endometrium (FHW S-56-1574). This particular patient was treated for one month with diethylstilbestrol alone (5.0 mg. daily for 2 weeks, then 10.0 mg. daily for 2 weeks) and Fig. 4 (FHW S-56-2221) shows that ovulation had been inhibited and early cystic glandular hyperplasia was developing, together with an increase in the size and number of the arterioles. During the second month of therapy Delalutin was added in the dose previously outlined. Fig. 5 (FHW S-56-2835) shows the changes brought about by this progestational agent. A marked decidual transformation of the endometrial stroma has occurred, together with a reversion of the glands to an early proliferative, or more properly, a "resting" stage. The glands here are made up of a single layer of cuboidal cells, none of which shows mitotic activity. Thus in one month the glands, which had shown growth patterns tending toward hyperplasia after estrogen stimulation, now

Fig. 4.

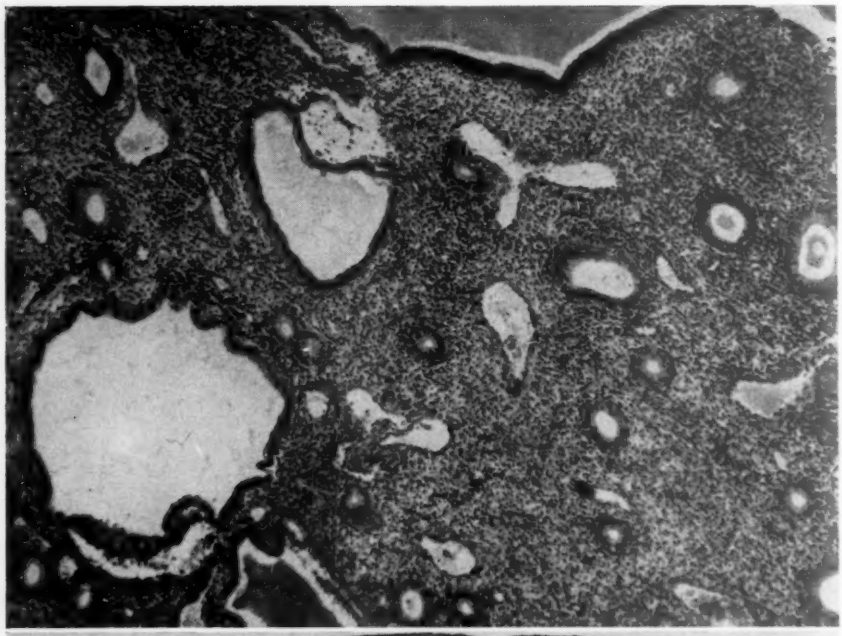

Fig. 5.

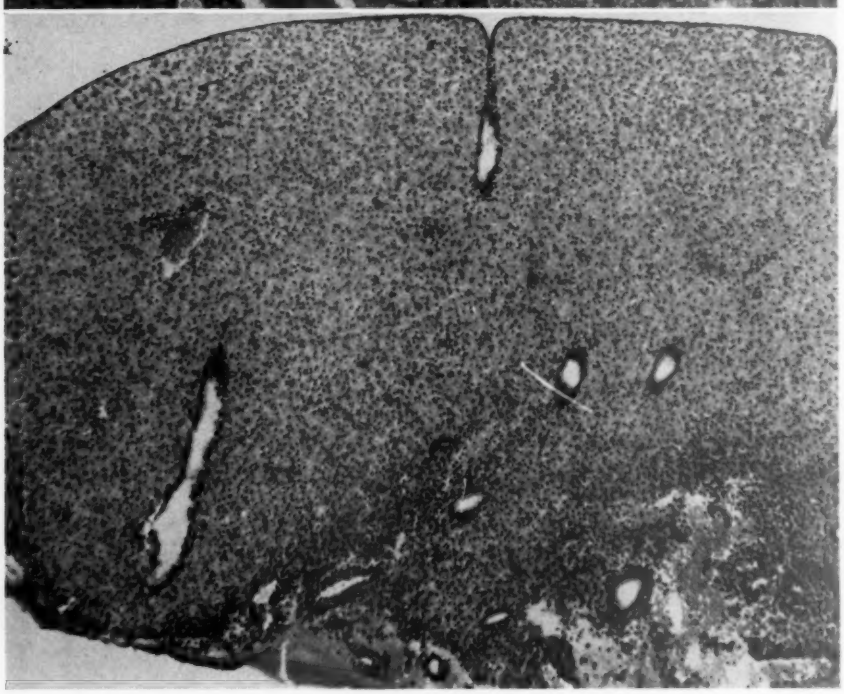

Fig. 4.—(FHW-S-56-2221.) Endometrial biopsy taken after increasing doses of diethylstilbestrol for 4 weeks. Note gland development with early cystic hyperplasia, dense stroma, and increased number and size of blood vessels. (×50; reduced ¼.)

Fig. 5.—(FHW-S-56-2835.) Endometrial biopsy taken after 4 weeks of increasing Delalutin and 8 weeks of diethylstilbestrol therapy. There is: (1) marked decidual transformation of the stromal cells, (2) glandular arrest with reversion of what was early hyperplasia, (3) diminution in number and size of blood vessels. (×50; reduced ¼.)

have become almost senescent in appearance despite the increasing biweekly dosage of diethylstilbestrol. This glandular change is similar to that found in the endometrium during the course of a normal pregnancy.

Fig. 6.

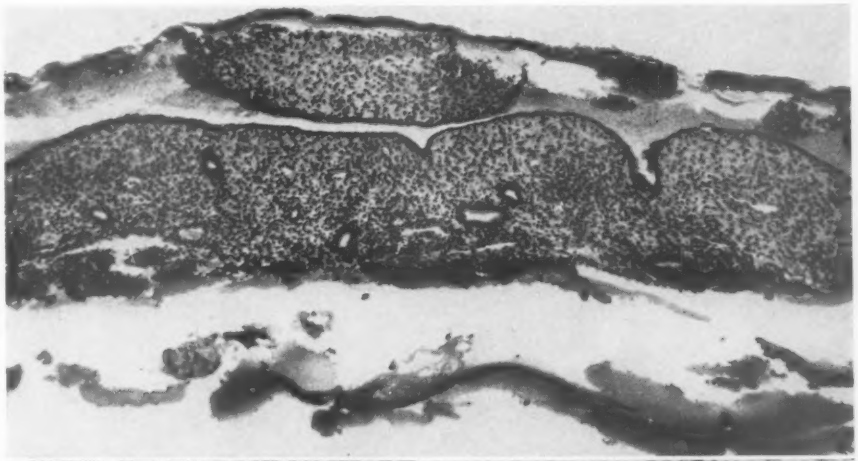

Fig. 7.

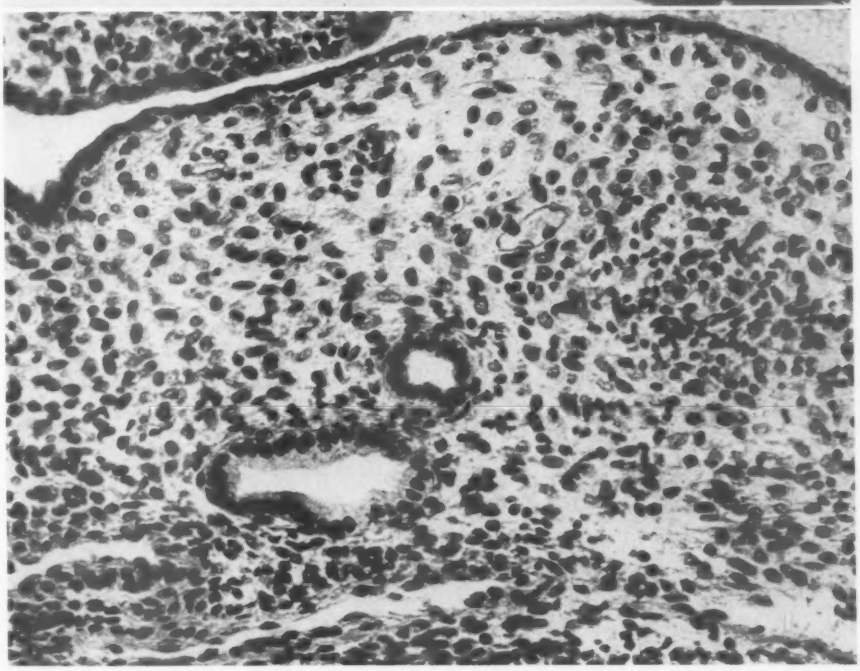

Fig. 6.—(FHW-S-56-3369.) Endometrial biopsy taken after 8 weeks of Delalutin and 12 weeks of diethylstilbestrol. Note: (1) decrease in total mass of tissue, (2) diminution in intensity of decidual reaction, (3) persistence of glandular arrest. (×50; reduced ¼.)

Fig. 7.—(FHW-S-56-3369.) A higher power of tissue seen in Fig. 7. Note that the glands consist of a single layer of cuboidal cells in a "resting phase," no mitoses being evident. In the upper right-hand corner is a group of lymphocytes around necrotic decidual cells. (×200; reduced ¼.)

Fig. 6 (FHW S-56-3369) illustrates further changes in the endometrium after 2 months of Delalutin and 3 months of diethylstilbestrol. At the time of this biopsy the patient was taking 60.0 mg. daily of stilbestrol and was being given 500 mg. of Delalutin weekly. Only minimal amounts of tissue were

obtained by the biopsy at this stage, as compared to one month previously when large amounts of tissue were easily obtainable. Here there is only slight to moderate decidual stromal effect, inactive endometrial glands, and focal areas of decidual necrosis. The latter is evident in Fig. 7 (FHW S-56-3369) which is a higher power of the tissue seen in the previous illustration. At this stage it seemed as though the endometrium was resistant to the effects of both hormones.

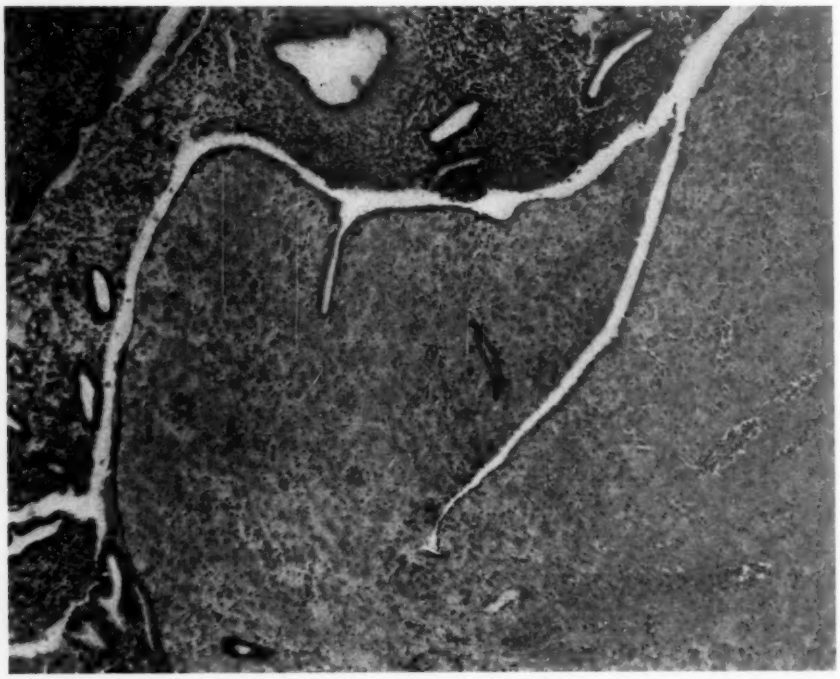

Fig. 8.—(FHW-S-57-528. Patient No. 5.) On the right side of the photograph is a typical area of decidual reaction in the endometrium of a patient who had a uterine curettage after 15 weeks of pseudopregnancy. There is focal decidual necrosis, glandular hypoplasia, and minimal vascular development. The endometrium in the left portion is proliferative and has not responded to progesterone. (×50; reduced ¼.)

Patient No. 5 (A. A.) progressed favorably during the therapy until the fifteenth week, at which time she began to have uterine cramps and bleeding. Because of the severity of the bleeding a dilatation and curettage was performed. Examination at this time showed the cervix to be soft and 3 cm. dilated with necrotic decidua in the patulous os. The uterus (which prior to treatment was in fixed third-degree retroversion) was soft, globular, anterior, and enlarged to a size equivalent to that of a normal 12 weeks' gestation. Dilatation was not necessary but curettage produced a voluminous amount of soft, gray-pink tissue which microscopically proved to be decidua in various stages of preservation (Fig. 8, FHW S-57-528).

Plan II.—One patient (No. 6, M. H.) is at present under treatment with Plan II and has progressed to 4 months with only moderate uterine pain and slight, irregular vaginal staining. The endometrial biopsies obtained here do not differ appreciably from those seen in Fig. 5 although not as much endometrium was available for study. The clinical symptoms and signs outlined previously under Plan I were present in lesser degree in this patient.

Plan III.—Three patients were treated according to Plan III. Two completed 3 months and one completed 4 months of pseudopregnancy. Fig. 9 (FHW S-56-2605) demonstrates an endometrial biopsy obtained after 10 weeks of treatment in Patient No. 8 (R. H.). A marked decidual response with glandular inactivity is again noted. The signs and symptoms noted previously in Plans I and II were present in this group also, with the exception that nausea was less evident in the earlier stages of treatment.

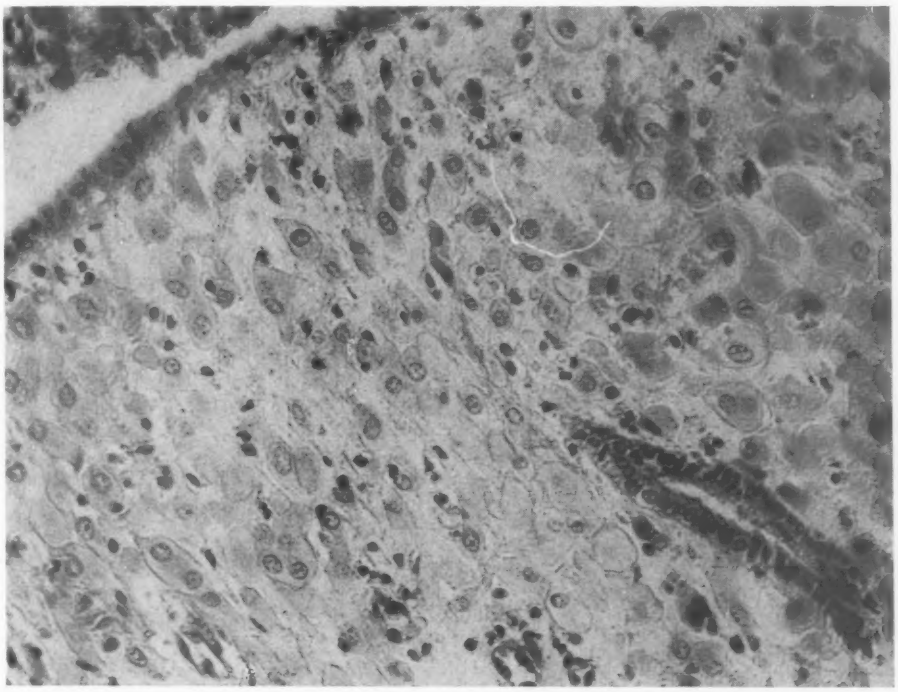

Fig. 9.—(FHW-S-56-2605.) An endometrial biopsy taken after 10 weeks of pseudopregnancy brought about by diethylstilbestrol and Enovid. Note the extensive decidual reaction and the inactivity of the one gland pictured at lower right. (×200; reduced ¼.)

Plan IV.—Two patients are currently under treatment with Plan IV. Patient No. 10 (I. D.) has extensive vaginal endometriosis (proved by biopsy) and has been receiving therapy for 4 months. Posttreatment biopsies have not as yet been obtained but symptomatic relief has been marked.

Patient No. 11 (E. J.) is a 27-year-old white nulligravida who was operated on in January, 1957, because of progressive, acquired dysmenorrhea and bilateral pelvic masses. At operation she was found to have extensive endometriosis involving both ovaries, the bladder peritoneum, the posterior cul-de-sac, and the serosa of the rectum. The uterus was in fixed retroversion and could not be freed. The left ovary was cystic and measured 5 by 6 cm. Because of the extensiveness of the disease the surgeon felt inadequate to do anything more than perform a biopsy on both ovaries since he felt the clinical condition might be due to extensive ovarian carcinomatosis. The biopsies, however, revealed active endometriosis. On the fifth postoperative day the patient was started on Enovid (10 mg. daily) and this was increased by 10 mg. every 2 weeks up to a maximum of 40 mg. which is being maintained. After 2 months of this therapy an examination under anesthesia and a uterine curettage were performed for diagnostic purposes. At this time no masses were palpable although there was moderate thickening of the broad ligament on the left side.

Fig. 10.

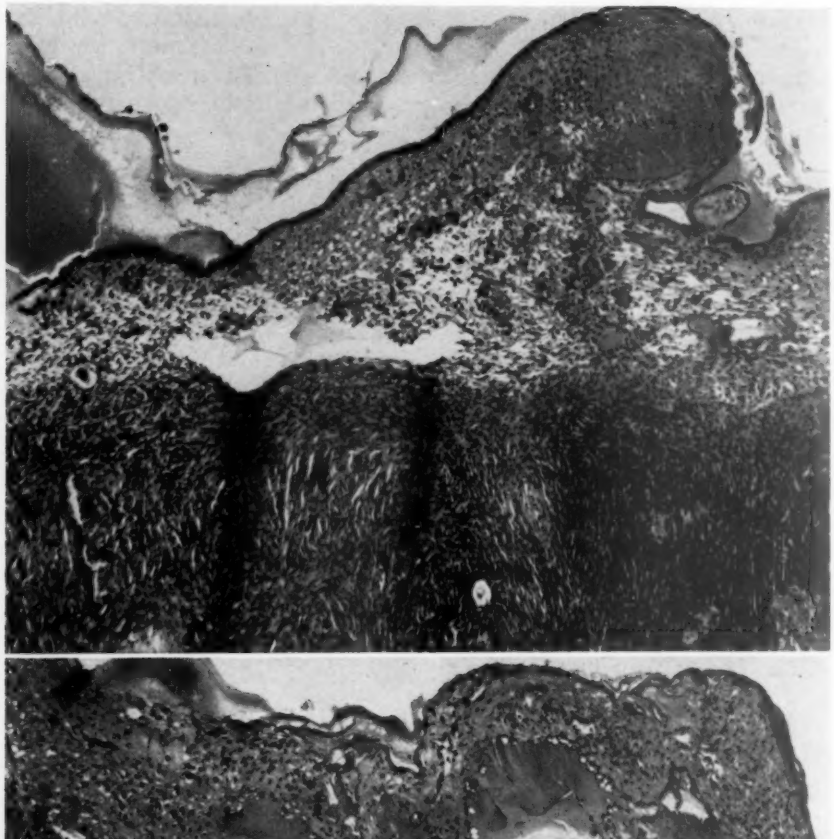

Fig. 11.

Fig. 10.—(FHW-S-56-4035, Patient No. 12.) Resected area of left ovary after pseudopregnancy with Delalutin and diethylstilbestrol and later Enovid alone. Under the surface epithelium there is an extensive decidual reaction in the stromal cells of the endometriosis. Closer to the ovarian cortex there are stromal edema and decidual necrosis. Several primordial follicles are seen in the dense cortex. (×50; reduced ¼.)

Fig. 11.—(FHW-S-56-4035, Patient No. 12.) Resected area of the left uterosacral ligament after pseudopregnancy as described in the legend to Fig. 10. The fibromuscular tissue of the ligament proper is seen at lower right and the greatly thickened endometriotic area above it. There are numerous thin-walled blood vessels, two glands at the extreme right, and an extensive decidual reaction with focal areas of necrosis throughout the endometriotic area. (×50; reduced ¼.)

The uterus was mobile and only one 2 cm. nodule was palpable on the left uterosacral ligament. Curettage produced a small amount of tissue which showed: (1) good decidual response, (2) glandular hypoplasia, (3) minimal vascular growth. It is planned to continue treatment for 9 months in this patient.

Patient No. 12 received combined therapy and is the only one in whom laparotomy was performed at the termination of treatment. This patient (D. D.), a 26-year-old white nulligravida, was seen in the outpatient department because of progressive, acquired dysmenorrhea and hypermenorrhea of 18 months' duration. A previous operation for an ovarian cyst had resulted in a right salpingo-oophorectomy for endometriosis. Examination disclosed extensive nodularity and thickening of the posterior cul-de-sac, a tender uterus in fixed third-degree retroversion, and a left adnexal mass with fixation. Therapy was initiated with diethylstilbestrol and Delalutin (Plan I). At the end of 10 weeks, crampy uterine pain and profuse bleeding occurred so that a uterine curettage was necessary. As in Case 5, profuse curettings were obtained which showed masses of necrotic decidua. At the request of the patient she was scheduled for operation but this was deferred for 6 weeks and during this time she was given 40 mg. of Enovid daily without estrogen. At the time of laparotomy another curettage was done which produced only minimal tissue. Examination showed marked softening of the cul-de-sac and adnexal area with relative mobility of the uterus. When exploratory operation was performed, the left ovary was found to be of normal size, loosely adherent to the posterior peritoneum and covered with ectopic "pseudo" decidua very similar to that found at the time of cesarean section. The cul-de-sac presented thickening and irregularity in the areas where the ovary was adherent. A presacral neurectomy, uterosacral denervation (with removal of segments of both uterosacral ligaments), left ovarian resection, and uterine suspension were performed. The resected ovarian tissue is seen in Fig. 10 (S-56-4035) and shows an extensive decidual transformation of the stromal cells of the endometriosis. There are focal areas of decidual necrosis. A segment of the excised uterosacral ligament is seen in Fig. 11 (S-56-4035) and shows similar decidual change with focal necrosis in the endometriosis overlying the ligament.

Comment

The present concept of treatment is predicated on the fact that pregnancy improves already existing endometriosis or prevents its development. Definite proof of both of these statements is lacking and the meager amount of available evidence is based on published observation by a few clinicians who have been interested in the subject. There is no doubt that during the period of the pregnancy itself the symptoms of endometriosis are alleviated. It cannot be denied, however, that such improvement is noted also during periods of induced anovulation whether brought about by estrogens or androgens.

Scott[16] and others have pointed out the relationship of pregnancy to endometriosis already present and have noted changes in endometriotic areas during gestation. There is no doubt that such changes are due to increasing and sustained levels of estrogen and progesterone and not simply to suppression of the pituitary. An example of the effect of normal pregnancy upon ovarian endometriosis is seen in Fig. 1. This patient, a 25-year-old nulligravida, was seen first in 1955 for acquired dysmenorrhea, dyspareunia, and rectal pain. By pelvic examination findings typical of endometriosis were present, apparently involving both ovaries. A pregnancy occurred subsequently which was terminated by cesarean section. At the time of this operation both ovaries

were noted to be extensively involved with "ectopic" decidua as was the posterior cul-de-sac. Attached to the left ovary was a dark brown, collapsed, cystic mass approximately 4 by 3 cm. in diameter. This was removed and is represented photomicrographically in Fig. 1. Here there is seen a decidual transformation of the ovarian stromal cells underlying the surface epithelium. These transformed cells are believed by Hertig, McKay[17] and others to be totipotential cells, derived from subcelomic mesenchyme (the same embryonic tissue from which the endometrial stroma develops) which may, under proper stimulation, develop into cells which have the appearance and function of endometrial stromal cells.

It is believed that this photomicrograph represents an area of stromal endometriosis which has undergone extensive decidual transformation with rather marked areas of necrosis. In the central portion of the photograph is a linear area which contains numerous hemosiderin-laden macrophages, old blood, degenerated endometrial stromal cells, and lymphocytes—a picture frequently seen in the wall of a "burnt-out" endometriotic cyst.

The unpredictability of permanent relief in endometriosis following the use of estrogenic substances alone has become apparent to us during the last few years. This may be due to the fact that some areas of endometriosis do not respond to estrogenic substances as well as the endometrium does. Or perhaps the temporary improvement with estrogens is mediated via the pituitary through suppression of ovulation. Scott and Wharton[18] have suggested that the growth of endometriosis is roughly proportional to the number of episodes of progesterone withdrawal from an estrogen-primed endometrium. Estrogen therapy also has the disadvantage of occasionally resulting in rather profuse "break-through" bleeding, endometrial hyperplasia, and hypermenorrhea at the time of withdrawal of the hormone.

Androgenic substances, while adequately documented as having produced desirable results in endometriosis, probably exert their effect through inhibition of gonadotrophic substances, although direct effect of the substance upon the endometriotic areas has been suggested. The undesirable side effects of hirsutism, acne, and deepening of the voice occur sufficiently often to cause the clinician and the patient considerable concern. The use of methylated preparations has also resulted in occasional hepatitis and jaundice.

In the series presented herein, only 3 of the 12 patients had endometriosis proved microscopically (2 pretreatment and 1 posttreatment). The objection may logically be made that such treatment was carried out in the absence of a positive diagnosis. This cannot be denied but in an effort to reduce the incidence of diagnostic error, all patients were selected for treatment by the author and all subsequent examinations and biopsies were performed by him. The patients were not selected on the basis of history alone, since pelvic pain may be caused by such a multiplicity of factors including psychoneuroses. In all patients there was definite involvement of the posterior cul-de-sac and/or uterosacral ligaments with fixation of the uterus. Adnexal masses were present in some but not in all cases.

The combination of progestational and estrogenic substances in large and continuing doses has not, to our knowledge, been previously reported. It produced amenorrhea as well as a decidual reaction in the endometria of all patients. In one patient operated on at the termination of therapy a decidual reaction was noted in the areas of endometriosis subjected to biopsy and it is assumed that this occurred in the other patients. All subjects were improved during the period of their pseudopregnancy both subjectively and objectively except for the few who noted crampy uterine pain and hypermenorrhea.

Whether this temporary improvement will be semipermanent or permanent will depend upon careful observation and examination during the next few years.

In future cases the use of culdoscopy to make certain of the diagnosis prior to treatment may be useful. Variation of dosage of both drugs to prevent uterine pain and "break-through" bleeding is now being studied. It is possible that better results could be obtained by eliminating estrogenic substances entirely since, in the presence of adequate endogenous estrogen, a decidua may be produced with the progestins alone. This method would accomplish anovulation, decidual transformation of the stroma, and possibly would reduce the growth of endometrial vasculature. In Cases 10 and 11 this is being tried. Neither of these patients has noted pelvic pain or bleeding.

Summary and Conclusions

1. Based on the assumption that normal pregnancy improves endometriosis both subjectively and objectively, a state of "pseudopregnancy" has been induced by administration of large doses of estrogen and progestins for periods of 2 to 7 months.

2. It is suggested that the changes brought about in endometriosis by pregnancy are a combination of (1) anovulation and amenorrhea, (2) decidual transformation of functioning endometriotic tissue, (3) decidual necrosis and absorption.

3. Decidua was produced in the endometrium of all patients as determined by endometrial biopsies and in the areas of endometriosis of the one patient subjected to operation at the termination of treatment.

4. Nine patients were subjectively and objectively improved during the period of pseudopregnancy.

5. No conclusions can be given regarding the long-term effect of this treatment at the present time.

6. Variation in dosage of both estrogens and progestins will be necessary for optimum effect.

7. The use of this method as prophylaxis against the development of endometriosis is discussed.

I wish to thank Dr. E. C. Reifenstein of E. R. Squibb & Sons for supplying Delalutin and Delestrogen, Dr. J. Wm. Crosson of the G. D. Searle & Co. for supplying Enovid (norethynodrel with 1.5 per cent ethynyl estradiol 3-methyl ether), and Dr. Robert W. Burlew of the Schering Corporation for supplying Estinyl.

The photomicrographs were prepared by Mr. Leo H. Goodman of the Mallory Institute of Pathology, Boston, Mass.

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INGUINAL ENDOMETRIOSIS

Report of Two Cases

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A RECENT article by Dormandy[1] has reported 3 cases of inguinal endometriosis and surveyed the literature. Since this seems to be a rare condition, we are reporting 2 more cases seen at the Buffalo General Hospital. Perhaps as more cases are reported, this lesion will appear not to be as rare as has previously been thought.

First Case.—Mrs. S. was a 34-year-old married woman who complained of a lump in the right groin, present for 5 years. The tumor made its appearance monthly one day before the onset of her menstrual period; it increased to walnut size, then gradually subsided and disappeared about 5 days after cessation of the flow. It was tender and more or less painful, but she had noted no discoloration. The mass disappeared completely between menstrual periods. The menstrual periods were normal, occurring at 28 day intervals and lasting 5 days. Physical examination seemed entirely normal, with no evidence of a lump or tumor at the time of the examination, 16 days after the onset of her last period. Pelvic examination seemed normal. A preoperative diagnosis of endometrioma was made.

Operative Findings.—There was a palpable nodule anterior to the right pubic bone near the midline about 0.5 cm. in diameter. This nodule was slightly movable and detectable only by palpation. It was attached to the distal end of the round ligament which passed through a small hernial sac protruding through the deep inguinal ring. The tumor was excised and the hernia repaired. No recurrence of symptoms has been noted after 7 years.

Pathological Examination.—The tissue fragment measured 2.5 by 0.5 cm. On section, the fragment showed a large pea-sized nodule which, also on section, had several cystic structures. Sections through the fragment labeled "round ligament" showed fibrous and muscular bundles with scattered endometrial cysts. The cysts contained a well-preserved endometrial type of epithelium with a moderate amount of endometrial stroma. There was distinct fibrosis about the cyst and some older blood resorption. In one place the endometrium within the cyst appeared rather polypous and the glands slightly tortuous, but no secretory changes were evident (Fig. 1).

Second Case.—Miss K. was a 36-year-old nullipara. For nearly 8 years she had noted a small suprapubic mass which seemed to be present at all times. With the onset of each period it enlarged, however; then gradually it diminished in size, only to enlarge again the following month. The mass seemed to be getting larger over the years. She admitted no dysmenorrhea and her menstrual periods were regular. She had been examined by a gynecologist 5 or 6 years previously for the same condition but he had recommended no therapy. Her menstrual periods occurred every 28 days and lasted 3 to 4 days. The most recent had occurred 8 days before operation.

The physical examination indicated a nulliparous introitus. Rectal palpation suggested a normal-sized uterus, anterior and movable. There was a 2 cm. slightly movable, irregular,

hard mass over the right pubic bone about 2 cm. from the midline. This was nontender and did not seem to be fixed to the bone. A diagnosis of endometrioma was made. No evidence of hernia or dilated inguinal ring was noted.

Operative Procedure.—Pelvic examination under anesthesia disclosed no evidence of endometriosis. An incision was made over the tumor and the tumor was excised. At the

Fig. 1.

Fig. 2.

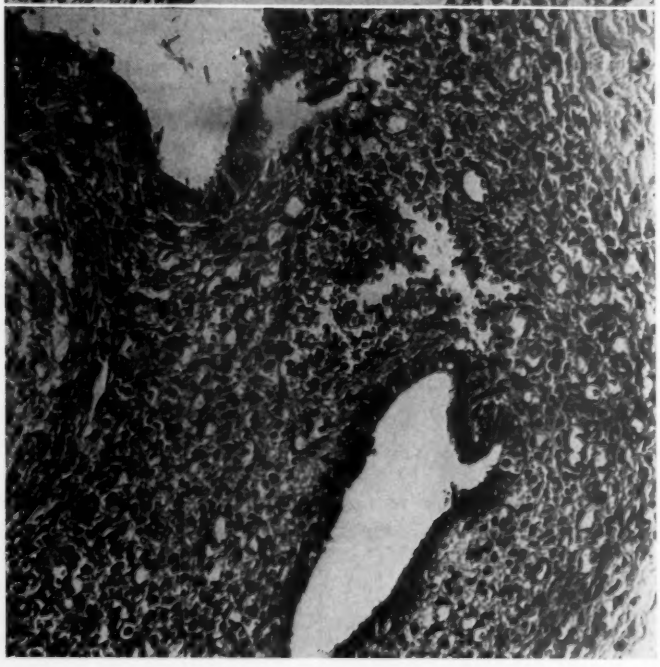

Fig. 1.—Section showing inguinal endometriosis in Case 1.
Fig. 2.—Section showing inguinal endometriosis in Case 2.

base of the tumor, however, there were a few small black areas suggesting endometriosis which could not be removed since they were densely adherent to the pubic bone. There was no hernial sac evident.

The patient was seen about a year later when she still had a very tiny tumor which still enlarged slightly during her period but was no longer troublesome.

Pathological Examination.—The tissue mass measured 3 by 2 by 1 cm. On section, there was a somewhat hemorrhagic mass about 1.5 cm. in diameter. Sections showed an area of endometriosis in fibrous and fat tissue. There was moderate inflammation in the surrounding tissue (Fig. 2).

Comment

Unlike Case 1 and the cases reported by Dormandy, in Case 2 there was no dilated internal inguinal ring or hernia, and it seems certain that this was an instance of an extraperitoneal lesion, a less common variety than the intraperitoneal type. Dormandy states that 12 of the 15 lesions reported individually in the literature occurred on the right side as did the 2 we are reporting.

It is interesting to speculate on the cause of the pain in both of our patients and even more severely in those of Dormandy. Sturgis and McCall[2] came to the conclusion that pain in peritoneal endometrial lesions was probably due to the distention caused by bleeding within a densely fibrotic lesion and that fibrosis represents a foreign-body reaction which eventually becomes extensive enough to "encapsulate" bleeding areas. In all of the instances cited by Dormandy, and in the 2 cases we have observed, this mechanism seems to explain the pain.

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ADENOCARCINOMA OF THE OVARY WITH PROBABLE ORIGIN IN ENDOMETRIAL CYST

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ADENOCARCINOMA of the ovary and ectopic endomentrium in the ovary are frequently seen in the operating room and in the pathology laboratory. The association of the two lesions in the same ovary, or even in the same patient, is quite rare.

Russell,[1] in 1899, was the first to describe ovarian endometriosis; in his case the opposite ovary contained an adenocarcinoma. Sampson[1] believed that ectopic ovarian endometrial glands could give rise to adenocarcinoma, and, in 1925, he published his well-known criteria which must be fulfilled before this change is established. Sampson stated that both benign and malignant tissue must be present in the ovary and that the carcinoma must be seen arising from benign endomentrial tissue.

Less than 30 cases of ovarian adenocarcinoma associated with ovarian endometriosis have been reported in the medical literature. Of these, about one-half have been accepted by gynecological pathologists as meeting Sampson's criteria.

For a complete review of the literature on this subject, the reader is referred to the publications of Scott[2] and Hunter and Klein,[3] as well as the recent case reports of Postoloff and Rodenberg[4] and of Weinrod, Bagg, and Sharnoff.[5]

Case History

Mrs. S. W., No. 88649, a 38-year-old nullipara, was admitted to the Gynecological Service of Sioux Valley Hospital on Jan. 13, 1954, for operation. Her chief complaint was pain in the lower abdomen of about 4 months' duration. The pain was insidious in onset, localized in the left lower quadrant, with some radiation to the back, and was aching in nature. There was aggravation of the pain by activity, and the patient stated that, recently, some discomfort persisted while she was in bed. There was no relationship between the pain and the onset of the menses. Review of the systems was not significant. A pelvic examination done in 1948 had revealed a "retroverted uterus with tender ovaries in the posterior cul de sac." The patient had been married for fifteen years with no conception. Menses had begun at the age of 13, occurred every 28 days, and lasted 5 to 6 days. The last menstrual period had been on Dec. 9, 1953. There was no history of dysmenorrhea. The family history disclosed that the patient's mother died of carcinoma of the breast.

Physical Examination.—A soft, movable mass was palpable in the left lower quadrant about 5 cm. below the umbilicus. On pelvic examination, a soft mass about the size of a 16 to 18 weeks' gestation could be felt occupying the left side of the pelvis. A firm midline mass in the uterine area was palpable and could not be outlined or demarcated from the larger lesion. Speculum examination showed a clean nulliparous cervix in normal position.

Surgical Description.—Upon opening the abdomen, the uterus was found to be enlarged to the size of an 8 weeks' gestation and irregular in outline, due to the presence of several small subserous leiomyomas. A large pedunculated leiomyoma measuring about 4 by 6 cm. was attached to the uterine fundus. A large ovarian cyst filled the left side of the pelvis and

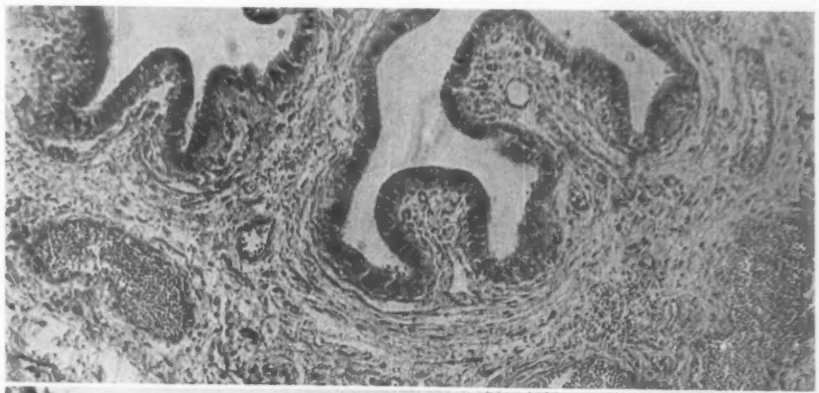

Fig. 1.

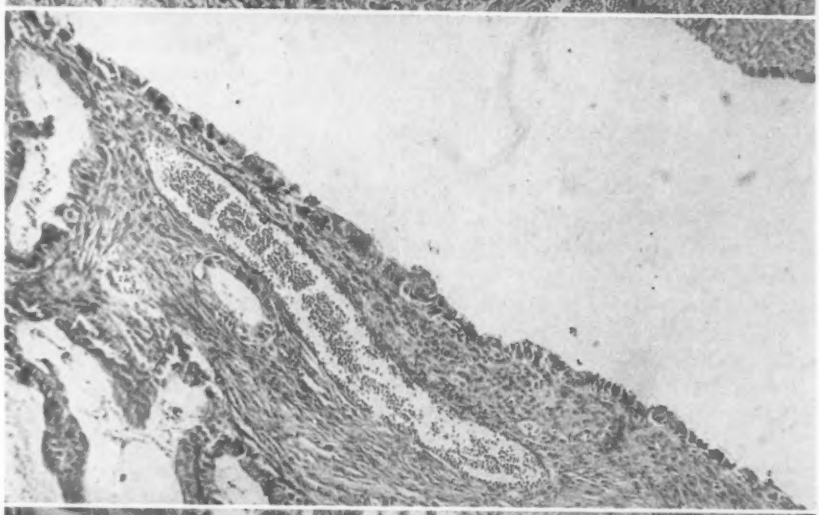

Fig. 2.

Fig. 3.

Fig. 1.—Ovarian cyst wall showing epithelium resembling that found in endometrium.

Fig. 2.—Epithelium showing anaplastic changes. Endometrial glands becoming malignant are shown in the lower left-hand corner.

Fig. 3.—Adenocarcinoma showing functioning glands and stroma like those of endometrium, and areas of squamous metaplasia.

was adherent to the posterior parietal peritoneum and the serosa of the rectum. During the dissection of the cyst, the cyst cavity was entered and a thick brown fluid was expelled. The right ovary appeared to be normal and was not removed.

Pathologic Report on the Left Ovary.—*

Gross: A cystic structure was submitted which was collapsed and measured 10 by 6 by 4½ cm., with a 4 cm. segment of Fallopian tube attached. In some areas the external surface was markedly corrugated. The open specimen showed a fungating yellowish-gray mass of tissue which measured 3½ by 3.3 by 2.2 cm. The large cystic structure, of which it formed a portion of the inner wall, was for the most part lined by trabeculated yellowish-gray tissue with areas of greenish-brown tissue.

Microscopic: Sections through the ovary showed laminated structures with very definite atypism of the epithelium, the cells varying moderately in size and character. In other areas there were small nests, cords, and strands of atypical epithelium. The cells and nuclei showed variations in size, configuration, and staining characteristics. There was increased chromatin clumping and increased prominence and number of nucleoli. An increase in mitoses was also found. In some areas of the supporting stroma there were infiltrations by lymphocytes and large mononuclear leukocytes to a moderate degree. The cells lining the cysts were much like endometrial cells and in areas endometrial supporting stroma was found (Fig. 1). The malignant cells originated from this epithelial tissue (Fig. 2). Sections through the remainder of the cyst wall showed areas of old and recent hemorrhage. The wall of the cyst was composed of dense eosinophilic connective tissue and, in areas, was lined by flattened cells.

Sections through the ovarian cystic structure showed it to be definitely adenocarcinoma arising in endometriosis. Endometrial tissue which lined the cavity of the cyst, showing good uniformity, could be traced to the area of carcinoma which was relatively localized, and which projected into the cavity of the cyst grossly. There was a gradual, not abrupt, transitional change from atypical cells to normal-appearing cells. In addition, in one section, definite squamous metaplasia was demonstrable in the columnar epithelium (Fig. 3). This again very strongly supported the origin of the malignant cells from endometrial tissue.

Comment

The presence of an ovarian cyst containing old blood in the cavity and endothelial leukocytes with poorly developed glands resembling those of the uterus in the wall leaves little doubt as to the endometrial origin of this ovarian tumor. The patient's long history of sterility and the associated findings of multiple uterine leiomyomas add further clinical evidence. Te Linde[6] stated that fibroids are associated with endometriosis in 53.7 per cent of cases.

Adenocarcinoma histologically resembling endometrial carcinoma and occurring as a papillary outgrowth in a localized area of this cyst is strong evidence that ectopic endometrium served as the original source of the malignancy. There were no anaplastic changes in the uterine endometrium which was in the proliferative phase. The presence of adenoacanthomatous elements in the ovary is also good evidence for the endometrial origin of the malignancy. Clinically this patient has remained in good health for 3½ years following her operation. This tends to rule out an extraovarian source of the carcinoma.

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*By Dr. C. B. Mitchell, Sioux Valley Hospital.

OVARIAN PREGNANCY AND ENDOMETRIOSIS*

A Case Report

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PRIMARY ovarian pregnancy is the rarest of all ectopic pregnancies, only 120 having been reported to date. Two of these had coexistent ovarian endometriosis. With the following report, there are now 3 cases, an incidence of 2.5 per cent of all ovarian pregnancies.

The criteria used for the diagnosis of primary ovarian pregnancy are those of Spiegelberg.[11] Further, this case was of the primary extrafollicular type, according to the classification based on site of implantation and development.[1]

M. D., a 32-year-old gravida ii, para i, was seen on April 21, 1956, complaining of sharp, stabbing intermittent paraumbilical pain, weakness, and syncope. The last normal menses commenced on Jan. 1, 1956. A skimpy menses occurred in February with no further vaginal bleeding until admission. Four weeks prior to admission, there had been a 2 day episode of severe, intermittent lower abdominal pain that subsided spontaneously. There was a past history of pelvic inflammatory disease noted first in 1954.

Examination revealed a pale white woman in acute distress. The blood pressure was 100/65, pulse 108 per minute, temperature 98° F. There was marked tenderness in both lower quadrants with rebound referred to the right lower quadrant. Voluntary guarding was present but no rigidity. Bowel sounds were normoactive. Pelvic examination disclosed a softened cervix, and an anterior soft, mobile corpus, enlarged to approximately the size of a 10 weeks' gestation. The posterior cul-de-sac was filled with a tense, tender, cystic mass, approximately 6 by 6 by 4 cm. The adnexa could not be well delineated.

Laboratory studies revealed a hemoglobin of 10.9 Gm. per 100 ml., a hematocrit of 31 per cent, and a white blood count of 13,700. A repeat hemogram 12 hours later disclosed 9.3 Gm. of hemoglobin and a hematocrit of 29 per cent. A tentative diagnosis of intrauterine pregnancy with an impacted hemorrhagic ovarian cyst was made and the patient was subjected to pelvic examination under anesthesia followed by celiotomy.

When the abdomen was opened, the peritoneal cavity was found to be filled with blood. The uterus was small, with a soft 5 by 5 by 6 cm. leiomyoma occupying the fundal area. The left oviduct and ovary were adherent to the broad ligament and lateral pelvic wall. The right oviduct was apparently normal. The right ovary was not grossly identifiable. The posterior cul-de-sac was filled with a soft, spongy, hemorrhagic mass consisting mostly of placental tissue. It was deemed technically impossible to resect the mass in the cul-de-sac and control bleeding without sacrificing the uterus, and hence a rapid supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. The subsequent postoperative course was uneventful.

*Presented at a meeting of the Chicago Gynecological Society, May 17, 1957.
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Fig. 1.

Fig. 2.

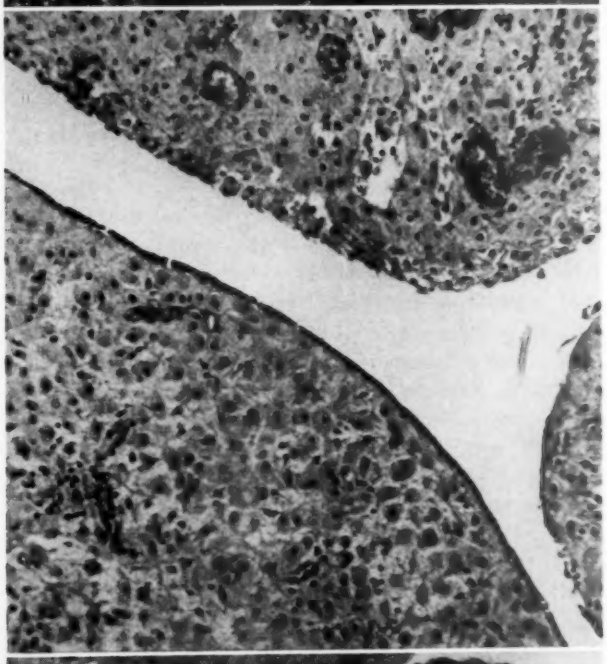

Fig. 3.

Figs. 1-3.—*For legends see opposite page.*

Pathologic Findings.—

Gross: The right ovary, measuring 6.3 by 4.5 by 2.2 cm., was irregular. On section, there was a large unilocular cyst in part filled with clotted blood. The lining of the cyst was smooth and glistening except for one large area of rupture. Adjacent to it there was irregular, hemorrhagic tissue to which the placenta, measuring 7.2 by 7.1 by 3.0 cm., umbilical cord, and fetus (crown-rump measurement of 4.5 cm.) were attached. The remaining ovarian stroma contained a large corpus luteum. The size, shape, and cut surface of the right oviduct were normal. The left adnexa was normal. The supracervically amputated uterus (340 grams) contained several large leiomyomas.

Microscopic: The right ovarian cyst was lined by tissue strongly suggestive of endometrium, apparently both glands and stroma (Fig. 1). The glands contained hemolyzed blood and debris, and the stroma had marked decidual reaction (Fig. 2) and abundant hemosiderin pigment. Numerous other areas in the left ovary and oviduct contained similar endometrium-like tissue with a structure virtually identical with that lining the endometrial cavity. A small portion of the left oviductal mucosa was also replaced by endometrium.

Lying almost in contact with the endometrial lining of the right ovarian cyst, and in most areas surrounded by ovarian stroma, there was a large mass of placental tissue consisting of viable, well-formed decidua and chorionic villi with abundant clotted blood (Fig. 3).

The pathologic diagnosis included right ovarian pregnancy; endometriosis with decidual reaction of the ovaries and left oviduct; leiomyomas of the uterus; and right oviduct with no pathologic diagnosis.

Comment

The case reported is a primary ovarian pregnancy of the so-called extrafollicular type in that the adjacent ovarian tissue contained an apparently intact corpus luteum.

The mode of implantation in this case is a matter of conjecture. Possibly the presence of endometrium within the ovary favored nidation of the ovum, as Gérin-Lajoie[5] stated. Maturation of the ovum within the oviduct is not considered necessary. The follicular ovum does undergo mitosis as part of the reduction division process.[8] Thus a stray virile spermatozoon could penetrate such an ovum, resulting in fertilization within the ovary. Such an event must have occurred in the case report of an ovarian pregnancy occurring 11 years after a vaginal hysterectomy, complicated postoperatively by an asymptomatic fistula of the vaginal vault.[6]

Bobrow and Winkelstein[2] believe pelvic inflammatory disease may be a basis for all extrauterine gestations. In the present case there was a history of such disease, without pathologic substantiation.

The marked decidual reaction described in the endometrium in the present case is noteworthy. Romney and associates[9] reported a 19.1 per cent incidence

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Fig. 1.—Unilocular ovarian cyst containing products of conception. Arrow at *A* represents cyst lined by a single layer of cuboidal to columnar epithelium, similar to endometrial lining, with subjacent endometrial stromalike components containing a marked decidual reaction. At *B* there is abundant hemorrhage. Beneath this (*C*) is a well-formed chorionic villus. (×10; reduced ¼.)

Fig. 2.—Another adjacent cyst wall lined by cuboidal to columnar epithelium with marked subjacent decidual reaction in the stroma. (×100; reduced ¼.)

Fig. 3.—A higher magnification revealing further cellular detail of a chorionic villus. (×100; reduced ¼.)

of decidual reaction with ectopic pregnancies, the remaining cases containing nondecidual endometrium that differs in no way from that seen in normal menstrual cycles.

The fetus was well preserved, indicating that rupture had occurred just preceding operation. Its crown-rump measurement was 4.5 cm. representing a gestational age of 10 weeks.[10] This first trimester termination is not unusual, because 75 per cent of ovarian pregnancies end then.[1]

Summary

A brief discussion of the classification, incidence, and criteria for ovarian pregnancy has been presented, followed by a description of a single case of the primary extrafollicular type. The possible pathogenetic role of ectopic ovarian endometrium is discussed.

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PROGESTATIONAL AND ANDROGENIC SUBSTANCES TESTED ON THE HIGHLY PROLIFERATED VAGINAL EPITHELIUM OF SURGICAL CASTRATES

II. Androgenic Substances*

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THE effects of androgen administration in human beings can be evaluated by the following methods: (1) clinically, by studies on male castrates, (2) biochemically, by excretion studies of the metabolites of androgens, and (3) cytologically, by evaluation of the epithelial changes in the vaginal smear.

The cytological effects induced on the vaginal epithelium by exogenous androgens will differ with the initial cell type and hormonal condition of the patient, and with the type of androgen used and the duration of treatment.

These initial cytological or hormonal patterns are considered for androgenic therapy:

A. Atrophic Menopausal Cell Type (Fig. 1).—If the initial cell type is characteristic of menopausal atrophy (predominance of parabasal cells), authors generally agree that administration of androgen will induce epithelial growth of the intermediate or superficial noncornified cell layers in the majority of cases.[1-7]

B. Nonatrophic Menopausal Cell Type (Fig. 2).—If the initial cell type in castrated or postmenopausal patients does not exhibit atrophy, but an intermediate state of proliferation, androgen administration usually causes no significant changes in epithelial growth. In some smears the occasional occurrence of higher proliferated cell types and also of deeper cells may be noted following androgen administration, but generally the epithelium does not respond to androgen treatment by growth.[3]

C. Markedly Proliferated Cell type (Fig. 3).—If the initial cell type is markedly proliferated, as seen with endogenous or exogenous estrogen activity, authors generally agree that androgen administration will result in regression of the epithelial proliferation to the noncornified cell layers.[5, 6, 8, 11]

D. During the Normal Menstrual Cycle.—In normal menstruating women, Papanicolaou and co-workers[9] were able to interrupt the normal cyclic development of the epithelium by administration of androgens and have reported

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a temporary regression of the epithelium from the fully proliferated state to the atrophic menopausal type, thus indicating temporary suppression of the ovarian follicular hormone activity.

Fig. 1.

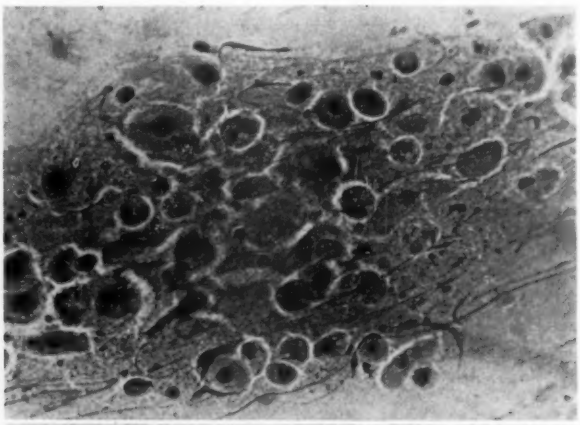

Fig. 2.

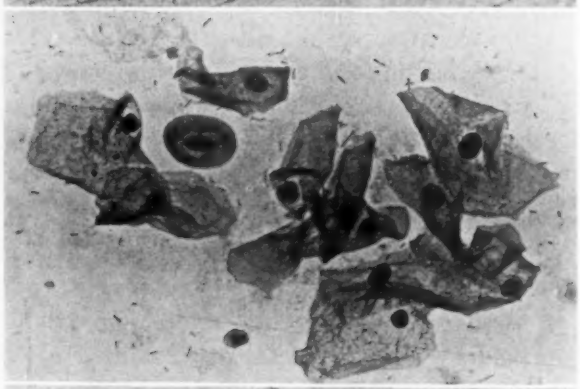

Fig. 3.

Fig. 1.—Atrophic menopausal cell type (10 years after surgical castration). The smear consists mainly of parabasal cells, abundant coccoid bacteria, and highly degenerated leukocytes.

Fig. 2.—Nonatrophic menopausal cell type (15 years after surgical castration). The smear consists mainly of superficial and intermediate cells, very few parabasal cells, very few leukocytes, and mainly *Bacillus vaginalis*.

Fig. 3.—Highly proliferated cell type in surgical castrate after 14 days of daily oral administration of 1 mg. diethylstilbestrol. The smear consists mainly of cornified superficial squamous cells, very few leukocytes, and mainly *Bacillus vaginalis*.

If androgen therapy is prolonged, i.e., cancer therapy, the effects must be more carefully considered since other factors, such as intercurrent infections, radiation cell changes, relatively poor vascularization of connective tissue, and the possible relationship between the tumor and the hormonal condition may render cytological interpretation difficult.

Fig. 4.

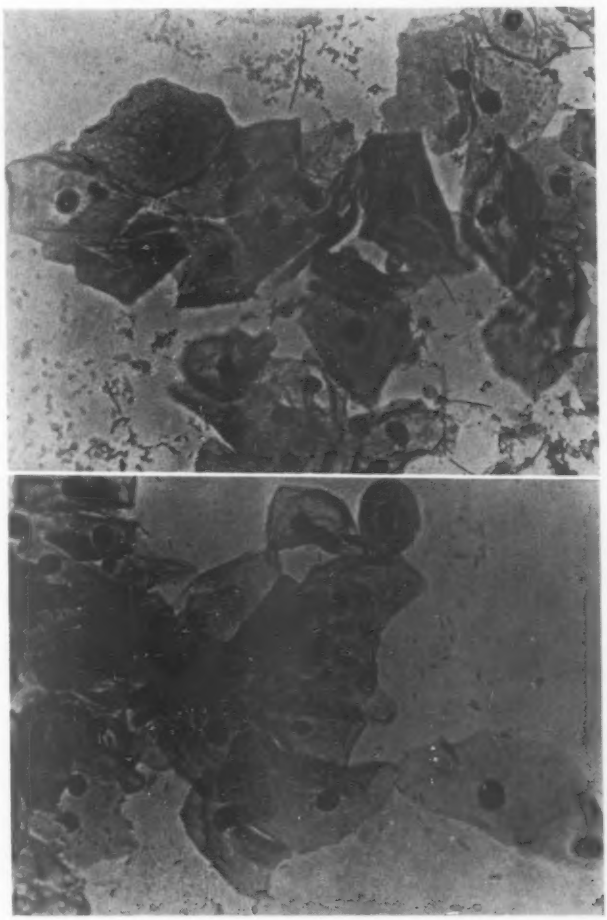

Fig. 5.

Fig. 4.—Result of androgen administration (150 mg. testosterone enanthate) in a surgical castrate who has been and is being treated simultaneously with estrogens (see Fig. 3). The smears show folded and moderately crowded superficial and intermediate cells, no leukocytes, mixed bacteria: epithelial *regression.*

Fig. 5.—Result of androgen administration (150 mg. testosterone enanthate) in a surgical castrate (Fig. 1) who exhibited previously an atrophic menopausal cell type and was not treated with estrogens prior to androgen administration. The smears show now mainly superficial and intermediate folded and moderately crowded squamous cells, very few parabasal cells, very few leukocytes, and mainly *Bacillus vaginalis:* epithelial *proliferation.*

In determination of the activity of androgenic substances, two cytological tests may be used to evaluate the degree and duration of androgen effects: (1) a proliferation test on an atrophic epithelium (Fig. 5), and (2) a regression test on an estrogen-stimulated epithelium (Fig. 4). For standardization

of results, it is suggested that surgical castrates without present or previous malignant lesions should be used for both tests.

The *proliferation test*[1, 3, 7, 14] yields reliable data only if patients with the atrophic vaginal epithelium (Fig. 1) are capable of good end-organ response. There is a distinct percentage of patients who will show a poor or negative end-organ response to administered androgens regardless of dosage. In such cases, the atrophic menopausal smear type will remain unchanged. In most of the patients with an atrophic menopausal type, however, proliferation following administration of androgens (Fig. 5) will resemble that produced by endogenous adrenal steroids[12] (Fig. 2).

The *regression test* will always yield positive results (regression of proliferation from cornified to noncornified cell layers) (Fig. 4) if the dosage of androgens is large enough to suppress the proliferative activity of simultaneously administered estrogens.

It is the purpose of this study to determine and compare the activity of two esters of testosterone, testosterone propionate and testosterone enanthate, as evidenced in the cytological regression test on the proliferated (estrogen-stimulated) vaginal epithelium of surgical castrates.

TABLE I. PROCEDURES EMPLOYED IN THE REGRESSION TEST

PATIENT NO.	AGE	YEARS POST CASTRATION	DOSAGE OF TESTOSTERONE PROPIONATE BY INTRAMUSCULAR INJECTION ON THE FOURTEENTH DAY	DOSAGE OF TESTOSTERONE ENANTHATE BY INTRAMUSCULAR INJECTION ON THE FOURTEENTH DAY
1	28	2	150 mg.	50 mg. 150 mg. 200 mg.
2	42	12		50 mg. 100 mg. 150 mg.
3	48	16	200 mg.	100 mg. 200 mg.
4	53	13		100 mg. 150 mg. 200 mg.
5	37	6	200 mg.	200 mg.
6	36	10	200 mg.	200 mg.
7	28	4	50 mg. 75 mg. 100 mg.	100 mg.

Material and Method

The study was performed on 7 surgical castrates with intact uteri. All patients had been under hormone therapy (estrogenic, or estrogenic and progestational) since castration. For the test, each patient received orally 1 mg. diethylstilbestrol daily through the 30 day test period. "Day No. 1" of the test period was arbitrarily fixed at the first day following the previous uterine bleeding. On the fourteenth day of estrogen therapy, each castrate

received a variable dosage of testosterone enanthate or testosterone propionate by a single intramuscular injection. The exact procedure is given in Table I.

Vaginal smears were prepared every third day during the test cycles, using the Papanicolaou method. The regressive effects of the androgens were evaluated cytologically.

Since there was no exact way of controlling the results histologically as in the previous study with progestational agents,[13] the patients were submitted to two cytological control tests:

(1) The patients received first a medication consisting of estrogens only: daily 1 mg. diethylstilbestrol orally through 30 days . Cytological smears were prepared every third day and the karyopyknotic, folded-cell, and crowded-cell indices recorded.

(2) The patients received the same medication as just described through the same period of time for another test cycle. However, on the fourteenth day, they received an injection of distilled water and were told that we had given them another hormone substance which would counteract the effect of the oral medication. Smears were prepared again every third day and the same indices were recorded.

The *cytological interpretation of the hormone effects* was made by cell counts of 300 cells on each vaginal smear: fifty cells were counted from each of six areas selected at random. Areas were evaluated only if the cells were spread thinly on the slide. Heavy clusters, apparently mechanically formed during the preparation of the smears, were not considered suitable for this study.

The three hundred cells were evaluated according to three indices: (I) the karyopyknotic index, (II) the folded-cell index, and (III) the crowded-cell index.[13]

To facilitate the interpretation of results, the degrees of epithelial regression are classified in the following groups:

(1) –, no regression.

(2) ±, slight regression, from the flat, single-lying cornified superficial cells to the slightly folded, less cornified cells; no appreciable cell crowding.

(3) +, moderate regression, to noncornified cell layers with a few cells of the intermediate cell layers in evidence; most of the cells show folding of cytoplasm, but only a minority of cells appear in crowded clusters.

(4) ++, marked regression, to noncornified superficial or intermediate cell layers. Practically all cells are folded and many cells lie in crowded clusters (this cell type is also often observed in surgical castrates or normal postmenopausal women who do not exhibit the atrophic menopausal smear type).

The *duration of cytological regression* was considered as the period of time during which the androgenic substance produced an active regressive effect upon the proliferation of the vaginal epithelium. This time was reckoned from the day when this epithelial regression was first detected until the day when the cellular pattern began recovery to the initial state of proliferation.

To facilitate evaluation and comparison of the effects of the two androgens, testosterone propionate and testosterone enanthate, curves for karyopyknotic, folded, and crowded-cell indices were plotted for every test cycle. Since the vaginal epithelium of surgical castrates who have been treated with estrogens prior to the test responded rather uniformly to a particular dosage of administered sex hormones, regardless of the age and the period of time elapsing since castration,[13] only the average curves are given to show the response to a particular dose of the esters (Figs. 6 and 7).

Results (Tables II and III)

A. Testosterone Propionate (Fig. 6).—A single intramuscular administration of 50 mg. testosterone propionate on the fourteenth day of one artificial cycle induced no regressive effect (–) on the proliferated epithelium; 75 mg. and 100 mg. testosterone propionate given by the same method induced slight regression (±) for a period of 3 days in both cases. While one intramuscular injection of 150 mg. testosterone propionate on the fourteenth day induced moderate regression (+) for a period of 3 days, 200 mg. induced moderate regression (+) in one out of 3 cases and marked regression (++) in 2 out of 3 cases, for a period of 6 days.

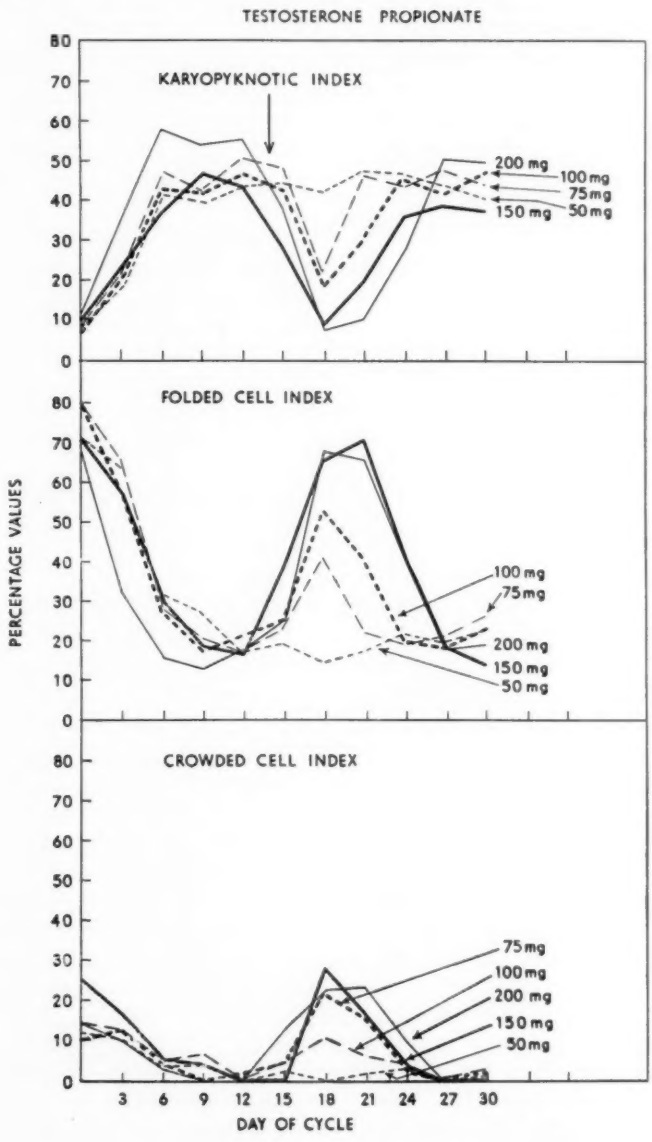

Fig. 6.—Average curves of the three cellular indices showing response of the highly proliferated vaginal epithelium of surgical castrates to various dosages of testosterone propionate administered by single injection on the fourteenth day of the test period. Each patient received daily 1 mg. diethylstilbestrol (orally) throughout the entire test period.

B. Testosterone Enanthate (Fig. 7).—One intramuscular injection of 50 mg. testosterone enanthate on the fourteenth day did not induce any epithelial change (–) in either of two cases. A single injection of 100 mg. testosterone enanthate on the fourteenth day induced, in one out of 4 cases, slight regression (±), and in 3 out of 4 cases, moderate regression (+), for a period of 3 days. The marked regression persisted for 9 days in 2 out of 3 cases with the injection of 150 mg., and in the one remaining case for 12 days. With the injection of 200 mg. testosterone enanthate, regression lasted in one case only for 9 days, while in the remaining 4 cases marked regression was induced for a period of 12 days.

The results of the cytological evaluation of smears performed as control tests showed (Figs. 8, 9) that the vaginal epithelium of the castrates reacted

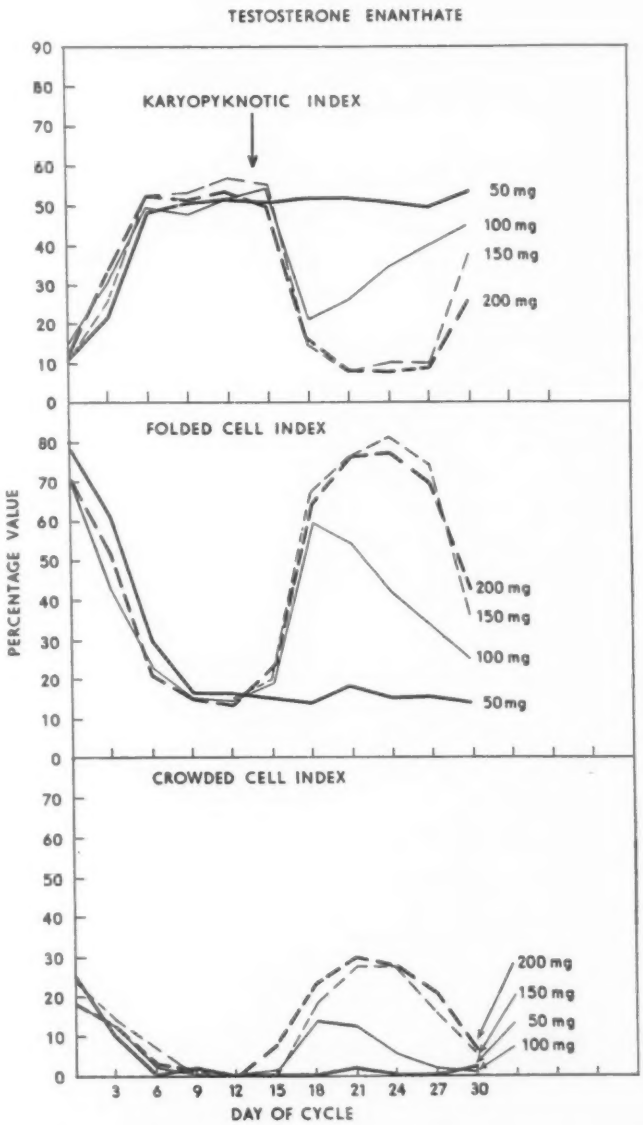

Fig. 7.—Average curves of the three cellular indices showing response of the highly proliferated vaginal epithelium of surgical castrates to various dosages of testosterone enanthate administered by single injection on the fourteenth day of the test period. Each patient received daily 1 mg. diethylstilbestrol (orally) throughout this entire test period.

to estrogenic stimuli with marked proliferation regardless of whether or not the patients were under the impression that they had received another hormone substance.

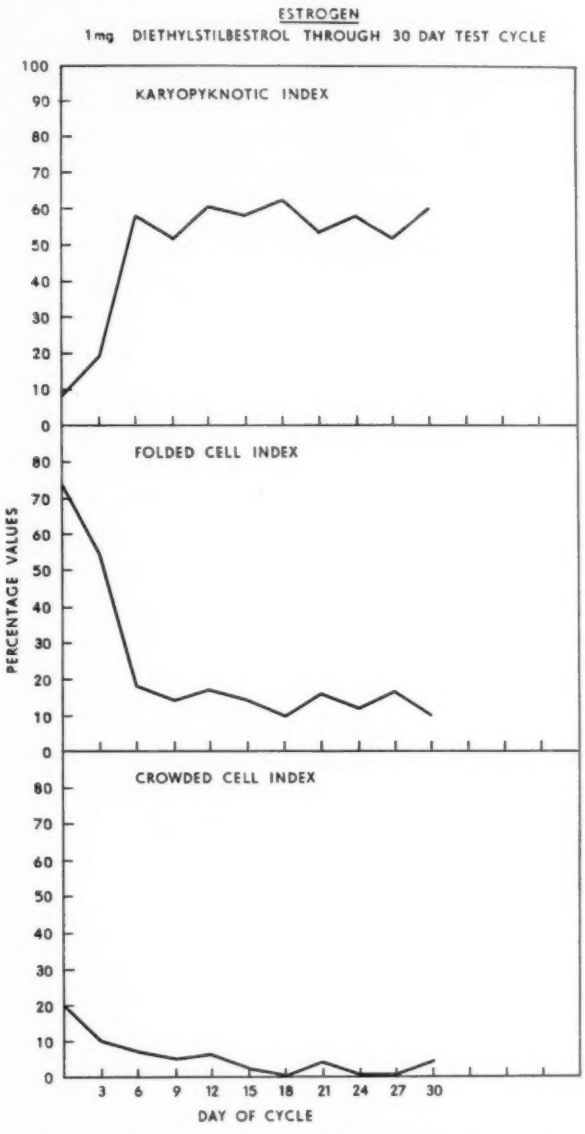

Fig. 8.—Average curves of the three cellular indices showing response of the vaginal epithelium of surgical castrates to 1 mg. diethylstilbestrol administered orally daily throughout a test period.

Comment

It is possible to determine the degree and duration of androgenic effects on the vaginal epithelium by means of the regression test. Although only a small number of patients are included in this study, rather uniform results were obtained.

The advantage of the regression test over the proliferation test is that the highly proliferated vaginal epithelium apparently will always respond

with regression to a sufficient dosage of androgens, whereas with the proliferation test a distinct percentage of patients with an atrophic epithelium (approximately 25 to 30 per cent) may not show any proliferative response. In the remaining 70 to 75 per cent of the cases, the latent period of proliferative

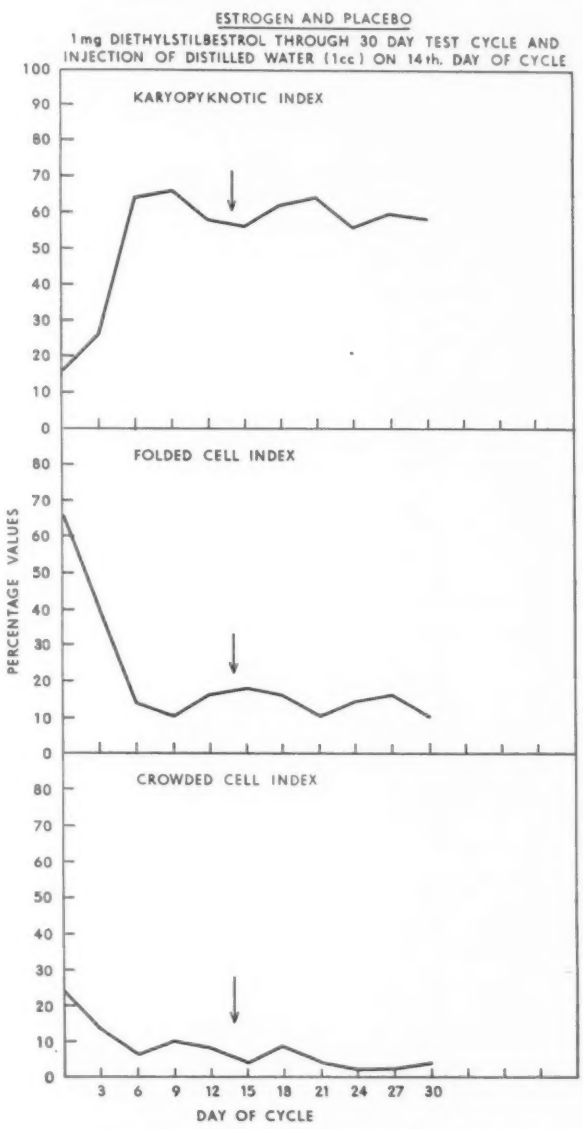
ESTROGEN AND PLACEBO
1 mg DIETHYLSTILBESTROL THROUGH 30 DAY TEST CYCLE AND INJECTION OF DISTILLED WATER (1cc) ON 14th. DAY OF CYCLE
KARYOPYKNOTIC INDEX
FOLDED CELL INDEX
CROWDED CELL INDEX
PERCENTAGE VALUES
DAY OF CYCLE
3 6 9 12 15 18 21 24 27 30

Fig. 9.—Average curves of the three cellular indices showing response of the highly proliferated vaginal epithelium of surgical castrates to a placebo (distilled water) administered by a single injection on the fourteenth day of the test period. Each patient received daily 1 mg. diethylstilbestrol throughout this entire test period.

response in the atrophic vaginal epithelium has to be considered. On the other hand, a disadvantage of the regression test is that the duration and degree of regressive changes are dependent on the proliferation dosages of exogenous estrogens. To fully evaluate the degree and duration of effects caused by androgenic substances, it seems advisable to use both the proliferation and regression techniques and compare the results.

In these studies, a single injection of 200 mg. testosterone propionate on the fourteenth day induced considerable regression of epithelial growth for a period of 6 days, whereas introduction of 150 and 200 mg. testosterone enanthate on the fourteenth day sustained the regression for 9 to 12 days. Regression might have been prolonged for a longer period of time with the same dosages of androgens had smaller quantities of estrogens been given to cause proliferation of the vaginal epithelium.

In consideration of these limitations, it might be stated that the actual duration of effects is not expressed in terms of hours or exact days. The results of the present regression tests show, however, that testosterone enanthate acts at least twice as long as testosterone propionate. These findings are corroborated by proliferation tests.[14]

Regression to atrophy did not occur as a result of androgen therapy in any of the 7 castrates. Parabasal cells were never observed in appreciable amounts among the higher proliferated cell types in the smears of the test patients. This finding may be attributed to the fact that androgen therapy was performed by single administration and not as long-term treatment.

TABLE II. DOSAGE EMPLOYED AND RESPONSE WITH TESTOSTERONE ENANTHATE

TEST CYCLE	YEARS POST CASTRATION	DOSES	CYTOLOGICAL RESPONSE		DURATION
1	2	50 mg.	–		
3	12	50 mg.	–		
47	4	100 mg.	±	during	3 days
10	12	100 mg.	+	during	3 days
23	13	100 mg.	+	during	3 days
16	16	100 mg.	+	during	3 days
3	2	150 mg.	++	during	9 days
11	12	150 mg.	++	during	12 days
24	13	150 mg.	++	during	9 days
43	10	200 mg.	++	during	9 days
4	2	200 mg.	++	during	12 days
25	13	200 mg.	++	during	12 days
30	6	200 mg.	++	during	12 days
17	16	200 mg.	++	during	12 days

TABLE III. DOSAGE EMPLOYED AND RESPONSE WITH TESTOSTERONE PROPIONATE

TEST CYCLE	YEARS POST CASTRATION	DOSES	CYTOLOGICAL RESPONSE		DURATION
44	4	50 mg.	–		
45	4	75 mg.	±	during	3 days
46	4	100 mg.	±	during	3 days
5	2	150 mg.	+	during	3 days
18	16	200 mg.	++	during	6 days
31	6	200 mg.	++	during	6 days
44	10	200 mg.	+	during	6 days

At the maximal point of regression (Fig. 4) or proliferation (Fig. 5) of the epithelium, the type of exfoliated cells is similar; the exfoliated cells are also similar to or identical with the cells usually observed during the normal menopause or after castration (Fig. 2), namely, the nonatrophic menopausal type.[8, 12, 15] It is suggested that the latter physiological type of intermediate proliferation may be caused by endogenous steroids of the adrenal glands.[12]

The present results support the general observation of Veziris and coworkers,[16] but not completely the findings of Rothermich.[17] In our opinion,

individual administration of androgens or progestogens induces, in the majority of the cases, cell growth of the noncornified intermediate or superficial cell layers, whereas estrogens induce, in all cases, proliferation of the cornified superficial cell layers. In this respect androgens and progestogens, as well as estrogens, act as synergists. On the other hand, androgens or progestogens administered simultaneously with estrogens suppress the proliferative effect of the estrogens to such a degree that the characteristic estrogenic effect upon the vaginal cells (cornification) does not occur. Since, physiologically, estrogens, androgens, and progestogens usually occur and act concurrently in the human female, it appears to be misleading terminology to speak only of gradations of estrogenic activity when describing the intermediate states of proliferation between the highly cornified and the atrophic cell types. Only these two latter cell types are in themselves diagnostic of hormone states; the one, for marked estrogenic activity; the other, for lack of estrogen stimulation of the vaginal epithelium. The intermediate states of proliferation, however, might be spoken of as being stimulated by the sex steroids, estrogens, androgens, and progestational substances, or by a combination of these hormone entities. It is possible, then, that the intermediate state of proliferation of the vaginal epithelium observed as a result of slight estrogen activity can be simulated when the proliferative effect of a considerable dose of estrogens is suppressed by either androgens or progestational substances.[13] Similar epithelial patterns can be observed where androgens alone produce cell growth in an initially atrophic smear type.[1-4, 8, 12, 14] With reference to the hormone reading of vaginal smears, these observations indicate that the intermediate stages of proliferation are not of themselves diagnostic of any definite hormone condition, but may be of relative diagnostic value if information on age, menstrual history, previous surgical procedures, and administered hormones is supplied.

Conclusions

1. A single dose of androgens administered simultaneously with daily dosages of estrogens produced in the vaginal smears of 7 surgical castrates regression of epithelial proliferation from the cornified (flat, single) superficial cells to the noncornified superficial or intermediate (folded, crowded) cells.

2. Two control tests were performed with estrogen therapy alone. During one of these tests the patients were told that they were given an injection of another hormone which in reality was distilled water. The cytological response of the epithelium was identical in these two control tests, however.

3. The degree of regression of epithelial proliferation may be used to determine comparatively the efficiency and active duration of administered androgens. Both the proliferation test and the described regression test can be used to determine the activity of exogenous androgens.

4. An advantage of the regression test over the proliferation test in assessing androgen therapy is that there will be an end-organ response in all cases. The disadvantage of the regression test is that the regressive effect of androgens is closely dependent upon the dosages of simultaneously administered estrogens. In this study, 1 mg. diethylstilbestrol was given daily per os. To obtain optimal results in testing the duration and the degree of androgenic activity of androgenic agents, it seems advisable to use both the proliferation and the regression tests.

5. A single parenteral administration of testosterone enanthate (200 mg.) suppressed activity of simultaneously administered diethylstilbestrol for about 12 days in 4 out of 5 cases when the daily dosage of oral estrogens administered was 1 mg. diethylstilbestrol. Epithelial regression in response to testosterone propionate (200 mg.) lasted only for 6 days in 3 out of 3 cases.

6. The occurrence of intermediate states of epithelial proliferation patterns in the vaginal smears are apparently not due solely to varying quantities of estrogenic substances.

Summary

The degree and the duration of androgenic activity of two esters of testosterone, testosterone enanthate and testosterone propionate, were evaluated and compared on the vaginal epithelium of 7 surgical castrates under estrogen therapy.

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INDUCTION OF OVULATION IN THE HUMAN: THERAPEUTIC AND DIAGNOSTIC IMPORTANCE

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THE management of ovulatory defects in the human has been varied but usually fraught with failure. It was felt that the lack of success in many cases was due to the fact that most of the procedures were not entirely physiologic or that insurmountable barriers to ovulation were present. This paper will present the rationale for, and results of, our attempts at attaining a more basic physiologic approach to the treatment of ovulatory defects and irregular menses in young women. Obviously, an understanding of the normal physiology of the pituitary-gonadal axis must be considered in order to evaluate properly aberrancies in the interrelationships of these endocrine glands, and then to devise an optimum plan of treatment.

Current knowledge of the normal cyclic functioning pituitary-ovarian axis from menarche to menopause is depicted diagrammatically in Fig. 1. Here, follicle-stimulating hormone (FSH) from the anterior lobe of the pituitary acts as the trophic principle in ovarian follicular growth. As the follicle matures, the level of its secretory product, estrogen, rises until it reaches that critical threshold level at which it inhibits further release of FSH and stimulates release of the luteinizing hormone (LH). This is depicted in Fig. 1 where estrogen from the ovarian follicle, after reaching an appropriate level, trips the "trap door" of the luteinizing hormone (LH) compartment so that release of LH occurs. LH then initiates, or triggers, rupture of the mature follicle and formation of the corpus luteum. Ovulation having occurred, there is a release of the luteotrophic hormone (LTH) from the pituitary which serves to maintain the life and function of the corpus luteum. The corpus luteum, in turn, secretes progesterone which is required to prepare the endometrium for nidation. Progesterone, in turn, inhibits the premature release of LH so that supraovulation does not occur. Should conception fail to occur, the functional activity of the corpus luteum is short lived and, with its disintegration, the progesterone level falls and menstruation (progesterone-withdrawal bleeding) occurs. During this period of disintegration of the corpus luteum the beginning of the next cycle has already been initiated by the release of FSH and maturation of a new follicle. Theoretically,

then, a defect or alteration in any one of the stages—either pituitary or ovarian—of this normally sequential series of interactions can result in menstrual irregularities, ovulatory failure, and/or amenorrhea.

It was felt that well-controlled, specific hormone therapy in properly selected cases of failure of ovulation might artificially trigger the defective ovulatory mechanism, based upon the above concept of the normal sequential relationships between the pituitary gonadotrophins and ovarian hormones.

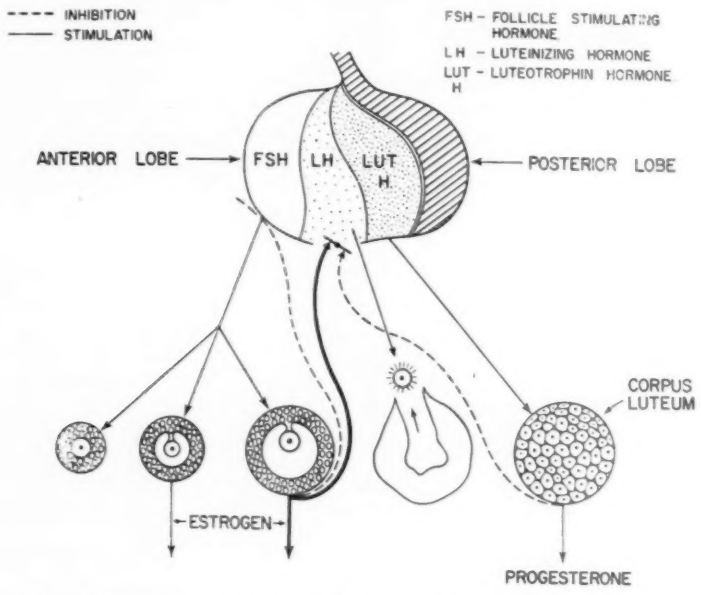

Fig. 1.—Diagrammatic presentation of normal reciprocal pituitary-ovarian relationships.

Rationale

Certain criteria for the selection of potentially responsive cases were established. Since the proposed therapy theoretically was to be specific for an isolated defect in ovulation, patients with other hormone imbalances that secondarily influence the pituitary-ovarian axis were not included in the series. Thus, each patient's thyroid and adrenal function was studied by the following tests, after a complete history and physical examination: protein-bound iodine, serum cholesterol, 5 hour glucose tolerance, and 24 hour 17-ketosteroid excretion. The anovulatory, euthyroid woman without evidence of increased adrenal cortical function was then instructed in the technique of recording her daily basal body temperature (BBT). In addition, the adequacy of ovarian function with respect to estrogen production, at least, was evaluated in patients with irregular menstrual cycles associated with oligomenorrhea or amenorrhea by noting the menstrual response in these women after an intramuscular injection of 100 mg. of progesterone in oil. Progesterone-withdrawal bleeding, occurring within 2 weeks of its parenteral administration, was taken as evidence of the presence of a proliferative endometrium, inasmuch as this steroid cannot induce menstruation unless the endometrium had been previously primed with estrogen.[1, 2, 3] This implies that the patient's ovaries contained sufficient follicle growth to secrete an adequate priming amount of estrogen upon which progesterone can then exert its secretory effect.

It should be noted that progesterone in the doses employed always induced a hyperthermic response in the BBT whether or not menstruation occurred. The hyperthermic effect, unlike menstruation, occurs regardless of previous priming with estrogen, so that the increase in BBT alone after exogenous progesterone cannot be taken as a measure of follicular-phase activity by the ovary.

The patients who had no menses after progesterone, and in whom persistent corpus luteal function or pregnancy was absent, were classified as probably having ovarian failure, gonadal dysgenesis, or endometrial failure, and were

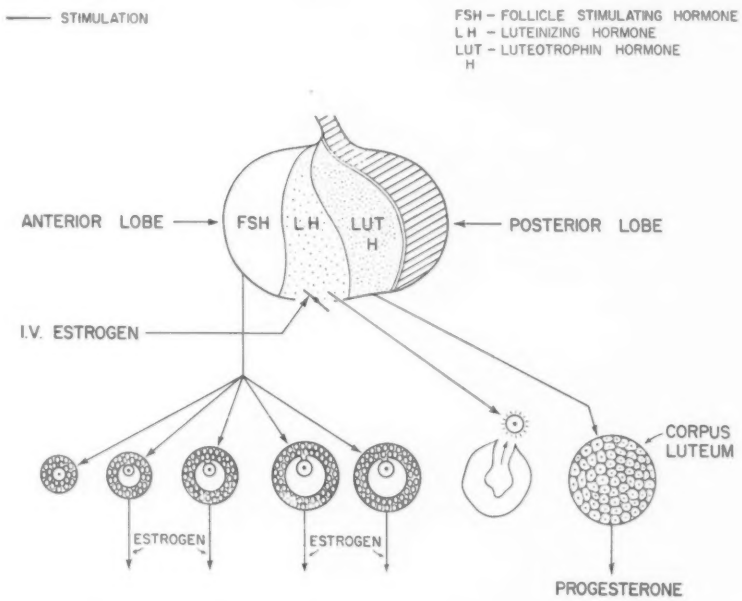

Fig. 2.—Diagrammatic presentation of the role of exogenous estrogen in inducing ovulation by stimulating release of luteinizing hormone.

studied further. These patients were not subjected to the procedures described below. On the other hand, the patients who were euthyroid with normal adrenal function and who menstruated fairly regularly or who menstruated after progesterone and showed an absence of pregnanediol with a flat BBT were judged as having ovulatory failure and fulfilled the criteria established for the "potentially responsive" cases.

With the postulation that failure of ovulation in these patients may be due to inadequately developed follicles incapable of releasing the critical threshold level of estrogen necessary for LH release (Fig. 2), it is conceivable then that one might be able artifically to trigger LH release with a large dose of exogenous estrogens, as depicted in Fig. 2. Experimental studies in single, immature parabiotic rats and some humans support this thesis. Fevold[4] postulated, on the basis of the effect of follicle-stimulating hormone in normal and in hypophysectomized rats, that estrogen from the FSH-stimulated follicle will release LH from the rat pituitary gland. Bradbury and associates[5-8] also showed by their studies that estrogens cause a degranulation of the basophilic cells in the pituitary gland and presumably a release of LH. Greep and Jones,[9] in the excellent review of their work on the effect of steroids on the pituitary secretion, suggested that estrogens may cause a release of both LH and FSH. Studies in the human,

based primarily on assaying gonadotrophic hormone secretion in normal and castrate women, have also demonstrated that estrogens can cause an increased release and secretion of LH and FSH.[10-13]

Methods

In order to demonstrate and utilize this premise in humans, those patients whose only endocrinopathy was failure of ovulation received 20 mg. of intravenous conjugated estrogens (equine) as a single dose, not sooner than the eighteenth day of the menstrual cycle, in order to avoid the possibility of confusing positive results of induction of ovulation with spontaneous ovulation. In some instances, intravenous estrogen was given as late as the fortieth day of the cycle and an ovulatory response obtained.

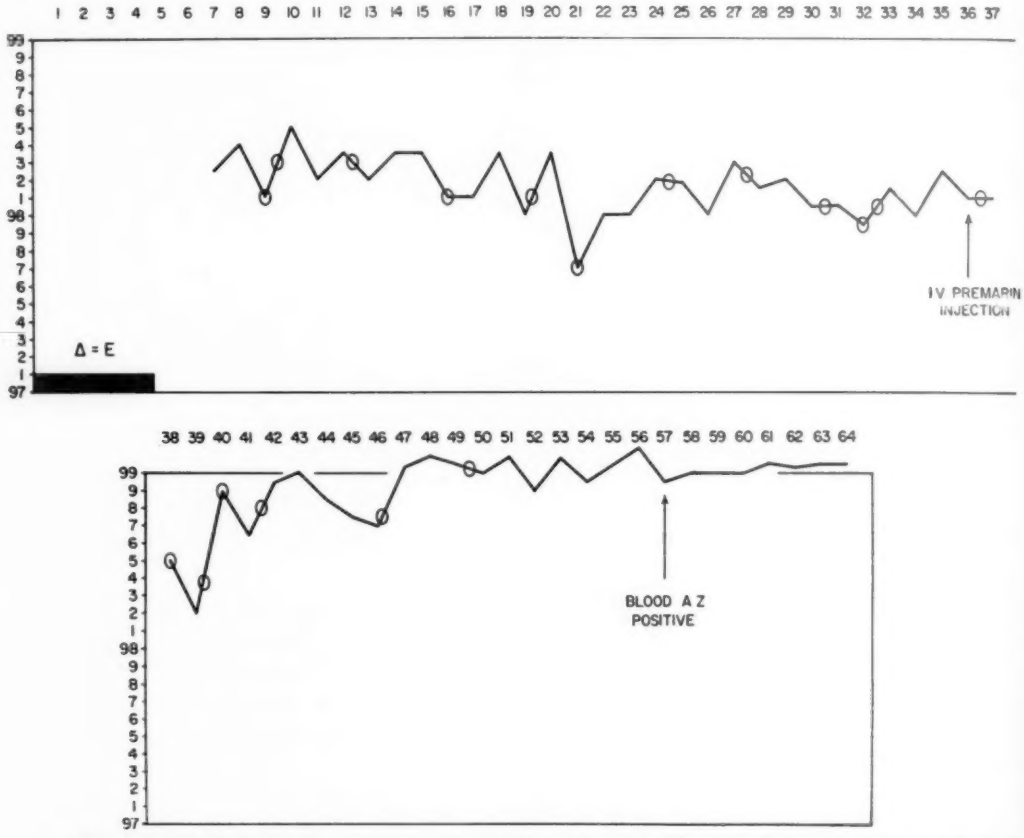

Fig. 3.—Basal body temperature chart of a 31-year-old anovulatory woman with a 3 year history of infertility which shows typical ovulatory response to intravenous estrogens characterized by temperature rise and conception.

$\Delta = E$ signifies proliferative endometrium of preceding menstrual period.

An ovulatory response was ascertained by (1) a significant rise in BBT, occurring in one to 3 days after the estrogen injection and lasting for at least 12 days, (2) an increased pregnanediol excretion 7 to 10 days after the injection, (3) secretory endometrium on endometrial biopsy on the first day of the ensuing menstrual period, or (4) conception. An elevation of the BBT alone was never accepted as proof of induction of ovulation. However, a secretory endometrium or cyesis occurring after the intravenous injection was accepted as evidence that ovulation had taken place.

TABLE I. PATIENT RESPONSE TO INTRAVENOUS CONJUGATED ESTROGENS (EQUINE)

PATIENTS	OVULATORY		NONOVULATORY (FOLLICULAR CYSTIC OVARIES)		UNDETERMINED BECAUSE OF INADEQUATE FOLLOW-UP
	NO. OF PATIENTS	NO. PREGNANT	NO. OF PATIENTS	DIAGNOSIS CONFIRMED BY OPERATION	
Infertility cases	17	9*	12	8†	2
Others	3	0	4	1	2
Total	20	9	16	9	4

*Average duration of infertility = 4.3 years (range 2-7 years).
†Three patients became pregnant after bilateral ovarian wedge resection.

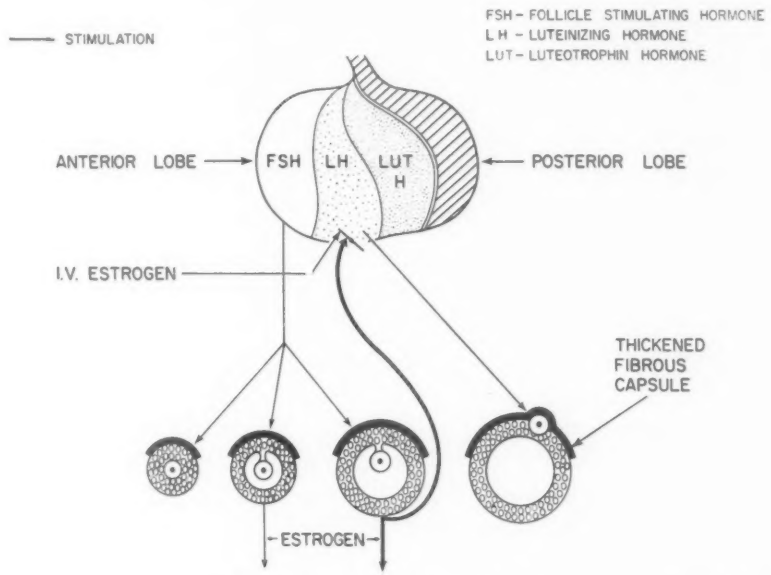

Fig. 4.—Diagrammatic presentation of the mechanical barrier to ovulation with either endogenous or exogenous estrogens, as seen in polycystic ovaries.

Results

Of the 40 patients treated with a single intravenous injection of 20 mg. of conjugated estrogens (equine), 31 were infertility patients and 9 were either single women with menstrual irregularities or married women practicing contraception with the same complaint. Wherever possible, endometrial biopsies were obtained on the first day of menstruation and showed persistent proliferative endometrium prior to the institution of therapy, thus confirming the diagnosis of ovulatory failure. In patients with prolonged amenorrhea, the prompt menstrual response to progestrone therapy also confirmed the diagnosis.

Table I shows the distribution of ovulatory responses among the patients in this series. Nine pregnancies resulted among the 17 infertile patients in whom ovulation was induced after no more than two estrogen injections, given at intervals determined by the patients' own basal body temperature charts. A typical ovulatory response in a previously sterile anovulatory woman is depicted in Fig. 3. The history of infertility in the 9 cases which resulted in pregnancy varied from 2 to 7 years, with an average duration of 4.3 years. It is of interest to note that one of the nonpregnant patients had her first *spontaneous* ovulatory menses in 3 years in the cycle *subsequent* to the intravenous estrogen-induced menses. Three other patients, with a history of only infrequently occurring spontaneous

ovulatory menses, also had normal 28 day cycles for one period following that induced by estrogen. Moreover, 4 of the 9 pregnancies occurred during the cycle subsequent to the estrogen-induced ovulatory response. From these data, one can deduce that the therapy was capable not only of inducing ovulation in the cycle in which it was administered, but was also effective in keeping the pituitary-ovarian cycle self-perpetuating at least for a limited time.

Fig. 5.

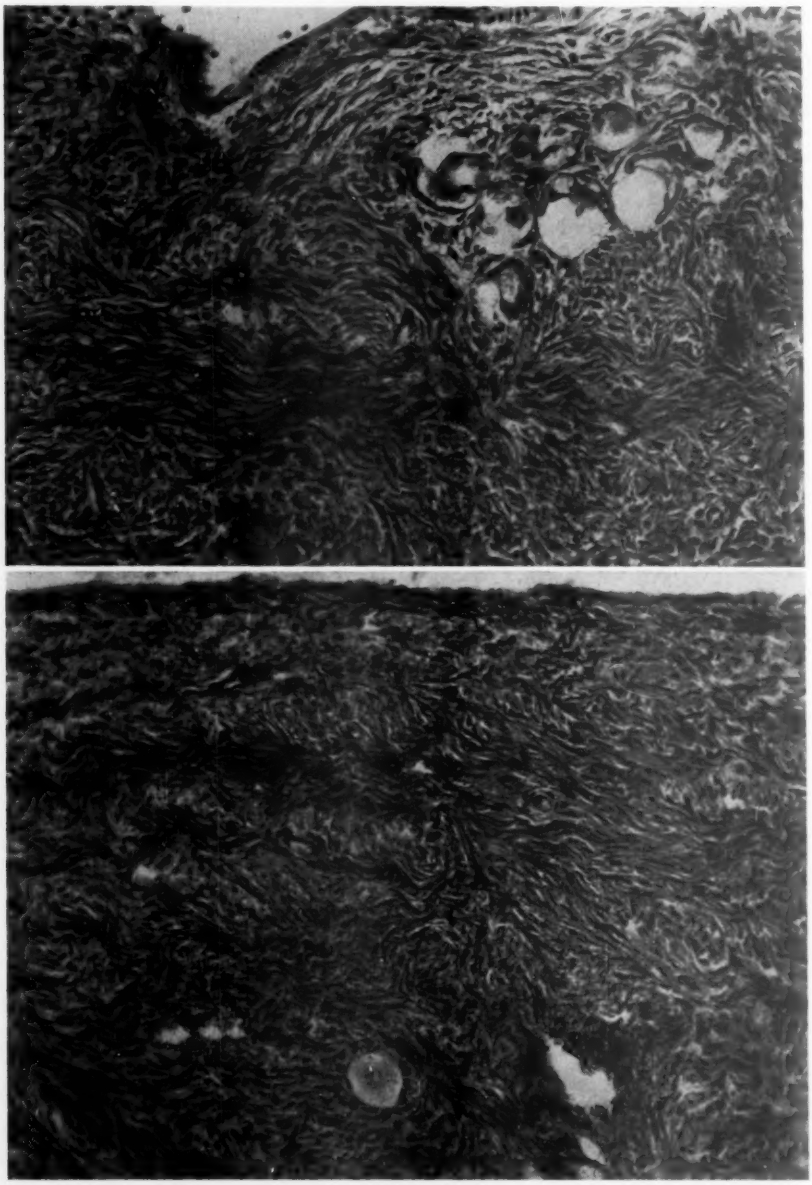

Fig. 6.

Fig. 5.—High-power microscopic section of ovarian tissue resected from patient A. G. Note thickened capsule and subcapsular cysts.

Fig. 6.—Section of ovarian tissue resected from patient M. S. Note the thickened fibrotic ovarian capsule.

To explain the negative responses among 16 patients, it was postulated that ovulatory failure was due to a mechanical inability of the ovary to respond to either exogenous or endogenous pituitary stimulation, i.e., polycystic ovaries of the Stein-Leventhal-like syndrome where the thickened fibrous tunica presents a mechanical barrier to ovulation (Fig. 4).

In these patients neither the endogenous estrogen levels nor the exogenous intravenously administered estrogens, notwithstanding their effect upon release of LH, were effectual in inducing ovulation because of the mechanical barrier presented by the thickened capsule.

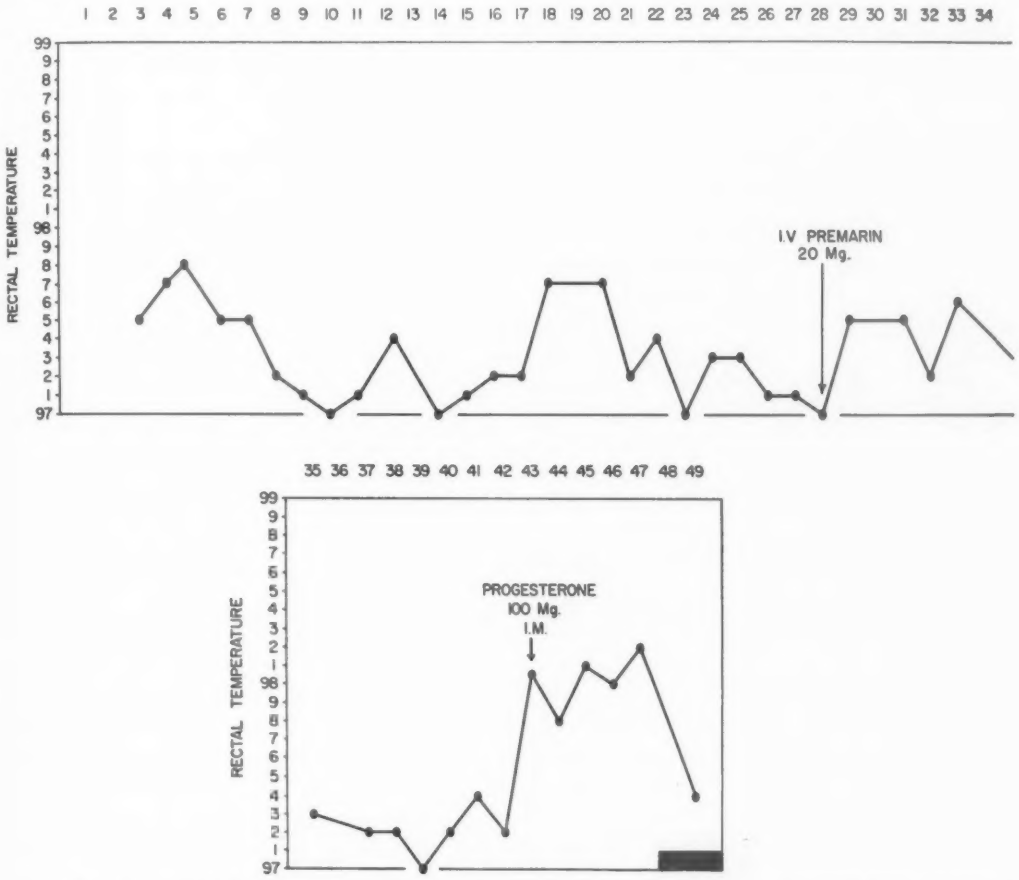

Fig. 7.—Basal body temperature chart of patient A. G., showing nonovulatory response to intravenous estrogens given on twenty-eighth day of cycle. Note hyperthermic and menstrual response to progesterone administered on forty-second day of cycle.

On this rationale, despite the absence of palpably enlarged ovaries on pelvic examination and the clinical stigmas set forth by Stein and Leventhal, surgical exploration with bilateral ovarian wedge resection was advised in 8 of the 12 infertile patients who were negative responders. Operation was suggested on the basis that all patients exhibited euthyroid and normal adrenal function associated with good proliferative activity, but with a lack of spontaneous ovulatory function, plus a failure of ovulation to follow at least 3 courses of intravenous conjugated estrogens administered as above. Figs. 5 and 6 show the histologic appearance of the respective ovarian tissue with the dense fibrous capsule resected from each. In each of the 8 cases that have come to operation to date,

the diagnosis of polycystic ovaries, made on the basis of the patient's failure of response to intravenous estrogen, was confirmed. Fig. 7 depicts the anovulatory temperature chart of patient A. G., in whom intravenous conjugated estrogens (equine) were ineffectual in altering the monophasic basal body temperature chart, yet menstruation readily followed the intramucular administration of 100 mg. of progesterone in oil. Each of the 8 patients had a bilateral ovarian wedge resection, following which they have all had regular menses save 3, who became pregnant.

Comment

The importance of the critical selection of the patients for the intravenous estrogen technique cannot be overemphasized. All the criteria of normal thyroid and adrenal function must be satisfied, as well as evidence of an adequate proliferative phase. Only then is the therapeutic and diagnostic use of the intravenous estrogen warranted, to induce ovulation in patients with a prolonged or irregular proliferative phase. In addition, the use of the intravenous estrogen as a preparatory procedure in patients who are candidates for artificial insemination, but who have an unpredictable ovulatory phase, may provide a technique offering a higher degree of success than in cases where dependence is placed upon the occurrence of spontaneous ovulation.

Use of intravenous estrogen as an aid in diagnosing a mechanical block to ovulation provides a tool with far-reaching potentials. The early stages of the Stein-Leventhal syndrome may not be classical, and the only manifestation of the disorder may be menstrual abnormalities characterized by the menorrhagia-amenorrhea syndrome, as seen in patients with ovulatory failure due to persistent estrogenic or proliferative activity. With the persistence of the blockage to ovulation, the follicular cysts may enlarge so that eventually palpable bilateral ovarian hypertrophy occurs, a finding characteristically seen in the advanced syndrome. Amenorrhea may ultimately intervene as a result of pressure necrosis of the ovarian parenchyma by the enlarging cysts. Some of the endocrine function of the ovary (estrogen production) thereby may be diminished or destroyed. Early diagnosis is possible by rigid adherence to the criteria listed above and, in the infertile couple, ovarian wedge resection despite the absence of enlarged ovaries may be the procedure of choice. Ovarian resection should also be considered in the young unmarried girl in whom progressive enlargement of the ovaries due to increasing size of the subcapsular follicle cysts may destroy enough ovarian parenchyma to diminish the endocrine function of the ovaries significantly. Section of the ovaries in such girls may salvage future ovarian activity and fertility.

Summary

1. In anovulatory women, with normal or medically corrected thyroid and adrenal function, ovulation may be induced by triggering the release of LH with a single large intravenous dose of conjugated estrogens (equine).

2. The early diagnosis of surgically correctable ovulation defects may be made on the basis of absence of an ovulatory response to this therapy.

Appreciation is expressed to Dr. John Jewell of the Ayerst Laboratories for the supplies of intravenous conjugated estrogens equine (Premarin) which were used in this study.

We gratefully acknowledge the clinical supplies of progesterone, 50 mg. per cubic centimeter in oil, that were provided by the following: Dr. H. F. Hailman of The Upjohn Company, Dr. Michael Carlozzi of Chas. Pfizer & Co., Inc., and Dr. George Babcock of Schering Corporation.

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HIDRADENOMA OF THE VULVA*

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THIS interesting type of tumor originates in sweat glands. The spelling "hydradenoma" is sanctioned by general usage. However, the correct form is "hidradenoma," since the derivation is from "sweat" and not from "water." These tumors have been observed in various parts of the body. In this paper, 10 instances of hidradenoma of the vulva are presented.

Historical Sketch

The first case of sweat gland tumor of the vulva was described by Schickele[1] in 1902. He thought the growth was of mesonephric origin. Pick,[2] in 1904, reviewed his paper and concluded that Schickele's tumor was of sweat-gland origin. Pick's exhaustive paper established conclusively the sweat gland origin of certain vulvar tumors. He reviewed 4 previously reported cases and added 3 of his own. This author described accurately the histological characteristics of these tumors and stressed the double layer of epithelial cells present in certain areas of sweat glands and in these tumors. He gave these growths the name "hidradenoma."

Other cases were then presented in foreign literature but it was not until 1915 that the first case was described in this country by Outerbridge.[3] Schwarz[4] reported the second case in America in 1921. The next paper on this subject did not appear in America until 1939, when Rothman and Gray[5] reported that there were only 40 cases described in the literature, only the 2 of these coming from the United States. These authors added 5 more. Subsequently approximately 100 more have been reported.

Types of Skin Glands

As an aid in understanding these lesions, it seems worthwhile to review briefly the various types of skin glands.

In general there are three types of glands[6]: merocrine, apocrine, and holocrine. Eccrine sweat glands are merocrine glands in which the epithelial gland cells remain intact during their secretory function. They produce a fluid which forms as little droplets within the protoplasm of the cells and then is secreted into the lumen of the gland without any loss of protoplasmic substance. Apocrine glands include in their secretion some of the cell cytoplasm,

*Presented at a meeting of the Chicago Gynecological Society, Feb. 15, 1957.

Fig. 1.

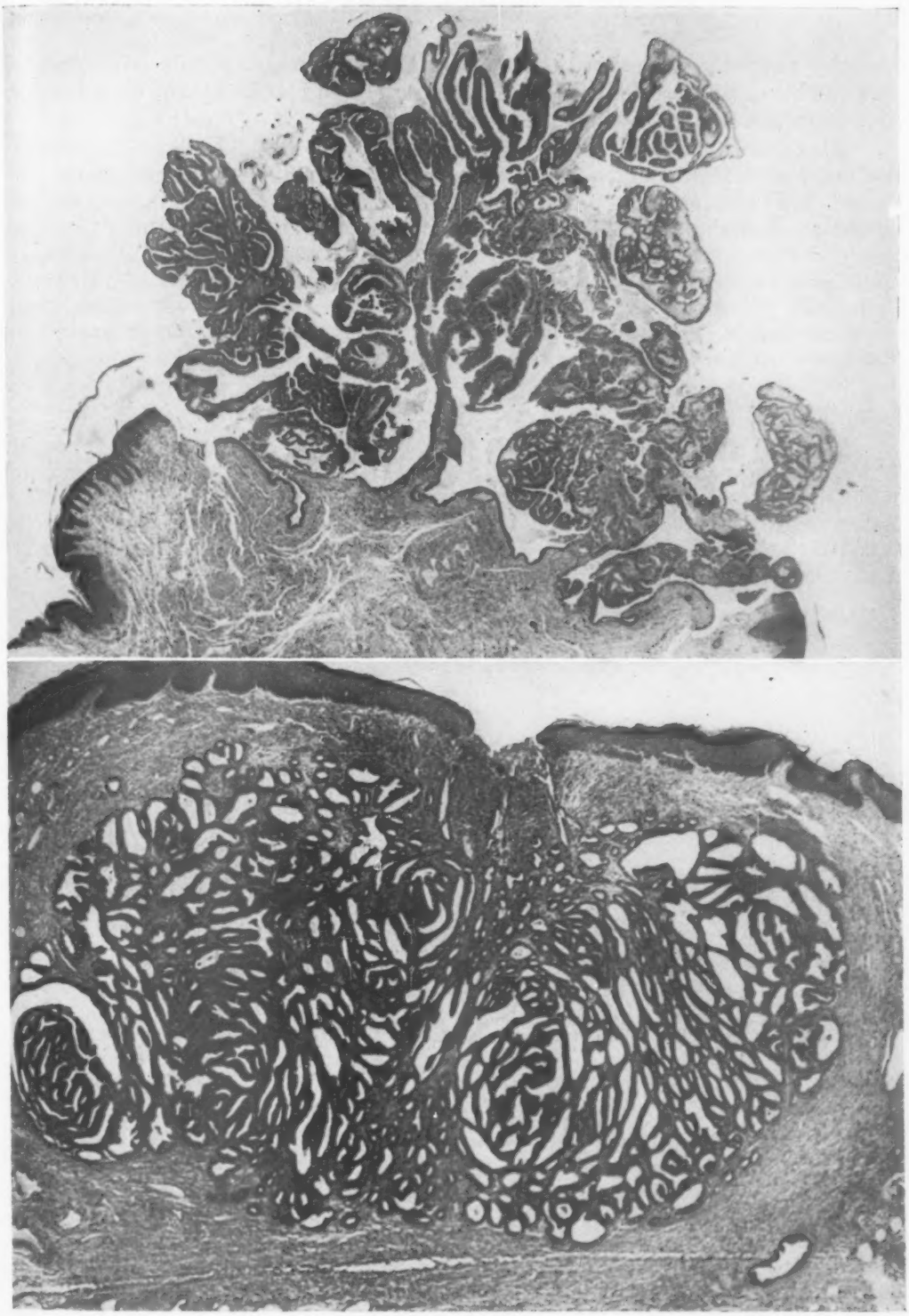

Fig. 2.

Fig. 1.—(N.U. Gyn. Path. 19975.) Hidradenoma showing protrusion of the papillary growth through the ulceration of the skin. Note the two types of eccrine and apocrine sweat glands present. (×27; reduced ⅙.)

Fig. 2.—(N.U. Gyn. Path. 16383.) Hidradenoma showing irregularly shaped and sized acini which are separated by delicate connective tissue septa. Note the small skin defect. (×36; reduced ⅙.)

thereby partially destroying themselves in the process. In holocrine glands, the epithelial gland cells degenerate completely and make up the gland secretion as in the case of sebaceous glands.

There are two types of sweat glands: eccrine and apocrine. Eccrine or ordinary sweat glands are scattered all over the body. Apocrine glands are found only in certain places: axilla, external earduct, nipples, vulva, abdomen, and the perianal area. Homma[7] stated that they are three times as numerous per unit of area in the Negro as in white people and twice as numerous in women as in men. While apocrine glands do not begin to function until puberty, they continue to function in old age. In women, function of these glands is reduced during the intermenstrual period, but increased in the premenstrual period and during pregnancy.

Histogenesis

There is general agreement on the concept first advanced by Pick that hidradenomas originate from sweat glands. He based his idea on the double layer of cells seen in certain areas of sweat glands as well as in these tumors. Between the surface epithelium and the basement membrane, Pick noted a layer of "ectodermal muscle cells." This so-called myoepithelial-cell layer was first described by Von Koelliker[8] in 1852. Until recently, relatively little

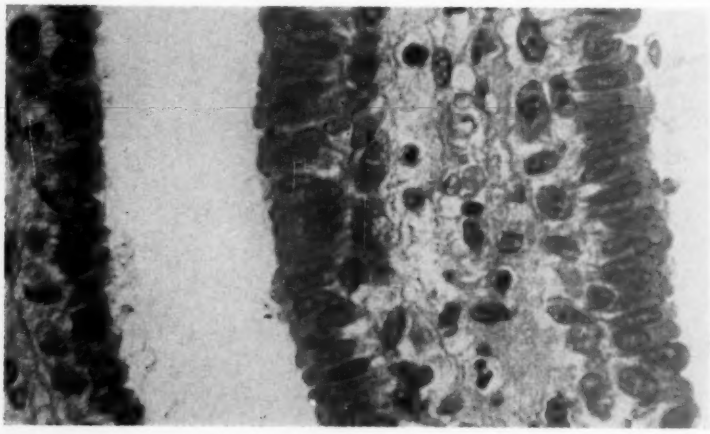

Fig. 3.—(N.U. Gyn. Path. 19975.) High-power photomicrograph of section showing two layers of epithelial cells covering a papillary projection. (×1,000; reduced ⅙.)

attention has been paid by pathologists to these contractile epithelial cells, although they have been known to anatomists for a long time. These myoepithelial cells are present in the mammary glands, the eccrine and apocrine sweat glands, Moll's glands of the eyelid, and in the cerumen glands of the ear. By their contractile function, they aid in expelling the products of the gland. Sheldon[9] in 1941 described these myoepithelial cells as spindle shaped, triangular on cross section, 30 to 90 μ long, with an elongated, rod-shaped nucleus and longitudinal cytoplasmic fibrils. Their morphological features and staining qualities are those of smooth muscle. Their longest axis runs parallel or slightly tangential to that of the gland. In apocrine sweat glands they form an almost continuous outer layer but in the eccrine sweat glands there are spaces between the single cells.

While the double layer of cells present in the acini of many hidradenomas of the vulva does not prove definitely whether the origin is from eccrine or

apocrine sweat glands, it does seem to exclude the possibility of sebaceous-gland origin. In general, however, it may be stated that most pathologists believe that hidradenomas of the vulva develop from apocrine sweat glands. This idea was first advanced by McDonald.[10]

Other than histological support for such an idea, clinical facts such as that (1) these lesions appear only in adult life and (2) they are found where apocrine glands are present help to confirm this theory. We must, however, agree with Novak and Stevenson[11] that there is often uncertainty as to whether or not the tumor arises from apocrine glands because intermediary histological types make differentiation between apocrine and eccrine glands difficult.

No present theory of pathogenesis explains the absence of hidradenoma of the vulva in the Negro, whose apocrine glands are three times as numerous as the white person's.[6, 12, 13]

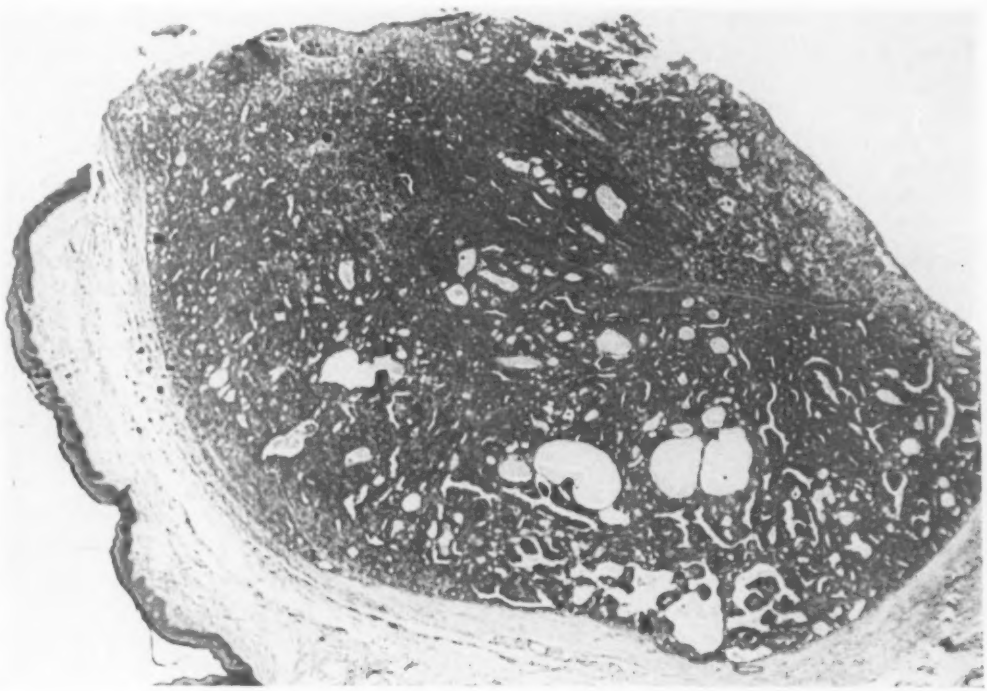

Fig. 4.—(N.U. Gyn. Path. 18868.) Hidradenoma showing marked adenomatous hyperplasia. Such lesions may be mistaken for adenocarcinomas. (×28; reduced ⅙.)

Histological Characteristics

Histologically, hidradenomas of the vulva are quite characteristic, although variations occur. They may take the form of cystic nodules in which the lumen of the cyst may be partially or entirely filled with papillomatous growths which may take origin from a broad base or from a single pedicle.

The general structure of this adenomatous lesion consists of innumerable irregular acini and tubules which are separated by delicate connective-tissue septa. Frequently, but not always, two layers of epithelial cells cover the papillary projections and line the acini. A layer of taller columnar or cuboidal cells lines the lumen of the acini. Each of these cells contains a vesicular nucleus situated at or near the base of the cell. The cytoplasm takes an acidophilic stain. The outer or second layer of cells is smaller with more

irregularly shaped, flat, spindle or cuboidal cells. These cells have small, dark nuclei with only a small amount of cytoplasm. This is the myoepithelial layer which rests on the basement membrane. This layer may be lacking in some of the acini, especially in the larger ones. In one of the 10 cases reviewed in this paper, the myoepithelial layer was only rarely seen among the numerous acini.

The acini vary in size and shape. Some are dilated. They are usually empty, although an occasional one may contain fine granular material or degenerated epithelium.

In the tissue of the 10 cases examined, evidence of generalized or focal acute and chronic inflammation was noted in every case except one. The degree of inflammation was more intense if the overlying epidermis was ulcerated.

Question of Malignancy of Hidradenoma

Marked hyperplasia of the adenomatous tissue of these growths has caused them to be mistaken for adenocarcinomas. This has been especially true whenever the acini are arranged in a more pleomorphic fashion or contain a few more mitotic figures.

In 1941 McDonald[10] of the Mayo Clinic reported 30 sweat-gland tumors of the vulva in 29 patients and considered all of them as malignant. Simple excision had been done in each case and none showed recurrence or metastasis.

Gates, Warren, and Warvi,[14] as well as Novak and Stevenson,[11] reviewed McDonald's paper and specifically stated that the majority of tumors described as adenocarcinoma of the vulva belong to the benign hidradenoma group. The latter two authors accepted only 2 of the tumors in McDonald's paper as malignant but stated that they were of unknown histogenesis as nothing in the descriptions suggested that they were of sweat-gland origin, although this possibility could not be ruled out. In supporting their disagreement further, they felt that it seemed incredible that, if the tumors were really adenocarcinomas, some recurrences or metastases would not have been observed in such a large group of cases treated by simple excision.

Novak further reviewed the original reports in the literature of the 4 cases considered malignant and he concluded that the cases of Ruge,[15] Schiffman,[16] and Burg[17] were benign. The only case in the world's literature at that time definitely showing malignancy developing in a hidradenoma was reported by Eichenberg.[18] It was described as an almond-sized nodule in the left greater labium which was widely excised with the tumor together with the left inguinal glands which showed definite metastasis. Novak went further to state that this adenocarcinoma may have arisen directly from sweat glands just as the benign hidradenoma does, and not necessarily with the intermediation of the latter. Allen and Fennel[19] speculated that Eichenberg's case could have been a Paget's disease of the apocrine gland of the vulva instead of a malignant hidradenoma. Plachta and Speer,[20] as well as Weiner,[21] of course, did report cases of apocrine-gland adenocarcinoma related to Paget's disease of the vulva.

Keasbey and Hadley[22] in 1954 reported 3 cases of "clear cell hidradenoma" with widespread metastases. The photomicrographs in this paper, however, showed tissue that had no histological resemblance to hidradenoma. These sweat-gland tumors may have been definitely malignant from the beginning and not necessarily have originated in or been a malignant change from benign hidradenomas.

The original pathological diagnosis in 9 out of the 10 cases being reported was hidradenoma of the vulva, 2 of them having the added diagnosis of possible adenocarcinoma because of pleomorphic proliferative glandular activity.

Mitotic figures were infrequent in all cases. The remaining or tenth case occurred in a patient who also had had a Stage II poorly differentiated adenocarcinoma of the cervix. Even though the gynecological pathologist originally stated that the tissue removed from the vulva appeared benign and different from the malignant tissue of the cervix, he still erroneously diagnosed it as metastatic adenocarcinoma of the vulva. He later, however, corrected the mistake and changed the diagnosis to hidradenoma of the vulva. This patient died 14 months later because of the cervical malignancy.

Clinical Features of Hidradenoma of the Vulva

According to the literature, this lesion is relatively rare; it must be true, however, that many of these growths are unrecognized because so many are asymptomatic and many others are erroneously diagnosed clinically and/or microscopically. Nine out of the 10 cases in the series reported here, were found since 1952. This only indicates that people now recognize this lesion and are looking for it. In the vast majority of cases the lesion is solitary, and rarely multiple. Cunningham and Hardy[23] reported upon one patient with several hidradenomas on each labium of the vulva.

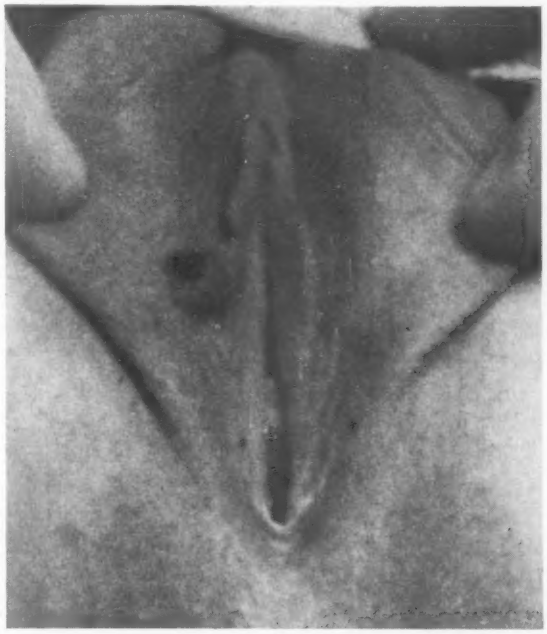

Fig. 5.—Hidradenoma of the right vulva showing the characteristic umbilication of the skin and the protruding papilloma. (Courtesy of Dr. John I. Brewer.)

Location.—They occur most frequently on one of the labia majora. Occasionally they are seen on the labia minora. In the present series, 3 cases were noted on the labia majora, 3 on the labia minora, one in the sulcus between the labia majora and minora, 2 on the posterior fourchette, and one on the perineum.

Size and Shape.—These lesions are well circumscribed, round or ovoid elevated nodules measuring from 0.5 to 1.5 cm. in diameter. Bruno and Meyer[24] reported a most peculiar case which they at first thought was a fibroid. This lesion was a 10 by 4 cm. hard, pedunculated mass of the right labium and within this growth was a hidradenoma 4.5 cm. in diameter. Most of the lesions in the present series were 1 cm. or less in diameter. Only one was 2 cm. in diameter. The smallest was 0.3 cm.

Umbilication.—With continued growth of the tumor, the pressure against the skin may eventually result in an ulceration of the overlying skin. When this break in the skin occurs, then the typical gross clinical picture is presented. This is mainfested as a tiny umbilication on top of an elevated mass and usually protruding through this opening is a red, granular, raspberry-like papilloma with a broad pedicle. It is only after this ulceration occurs that the clinical diagnosis of hidradenoma becomes obvious. Prior to this the elevated tumor mass is usually mistaken for a sebaceous cyst or fibroma. At times even in the presence of an umbilication of the overlying skin, this lesion is still mistaken for carcinoma or pyogenic granuloma of the vulva.

In the present series 6 of the 10 hidradenomas were diagnosed preoperatively because they showed the typical umbilication. Another one described as a small ulcerated lesion (0.8 by 0.8 cm.) was thought to be carcinoma of the vulva. Interestingly enough, one of these cases was followed for one year with the idea that the small tumor was a sebaceous cyst until a tiny hole appeared on top of the tumor. The diagnosis was then corrected; when the growth was "squeezed—out popped a papilloma."

In the 3 cases with intact overlying skin, 2 were thought to be sebaceous cysts and the other one, in the patient who had Stage II carcinoma of the cervix, was diagnosed purely from association as carcinoma metastatic from the cervix to the vulva.

Symptoms.—These lesions are usually asymptomatic except when ulceration of the epithelium occurs, in which case pain can be caused by infection. If a papilloma protrudes through the ulceration, then slight bleeding may occur. In the present series, 6 cases were asymptomatic; 2 were characterized by slight bleeding and 2 by soreness.

Age.—No cases have been reported prior to puberty. This condition occurs mostly in the 30 to 50 year age group. One of the oldest patients, reported upon by Danforth,[25] was a woman 77 years old. In McDonald's[10] large series of 30 cases, the age range was from 32 to 67. The youngest patient in the present series was 29 and the oldest was 64. A better concept of age range can be gained by study of Table I.

TABLE I. AGE RANGE OF PATIENTS WITH HIDRADENOMAS

AGE	NOVAK AND STEVENSON[11]	DEACON AND TAYLOR[26]	LENNOX[27]	PRESENT SERIES	TOTAL
Under 20	0	1	0	0	1
21-30	1	1	0	1	3
31-40	5	6	4	2	17
41-50	3	2	6	6	17
51-60	2	1	2	0	5
61-70	2	0	1	1	4
Over 70	0	1	1	0	2
No age given	2	0	1	0	3
Total	15	12	15	10	52

Treatment

Simple excision is the procedure of choice for hidradenoma because it is generally agreed that this is a benign lesion. Nine out of the 10 cases reported in this series were removed by this procedure and none has shown any recurrence or metastasis to date. Of course the patient with associated adenocarcinoma of the cervix died because of the latter condition in 14 months. The remaining case was thought to be a sebaceous cyst when discovered during

routine prenatal examination. The skin over the growth was "split" and the papilloma within the lesion was squeezed out. Even in this case there has been no recurrence.

Summary

Hidradenoma of the vulva is a relatively rare lesion that originates from apocrine sweat glands. It is generally agreed that this is a benign growth.

Ten cases of hidradenoma of vulva are presented.

We would like to express appreciation to Drs. George H. Gardner, John I. Brewer, George Bradburn, and Beatrice Tucker for permission to use their cases.

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Discussion

DR. ROBERT C. STEPTO.—In a review of vulvar tumors during the same period of time at Provident Hospital it has been interesting to note that, with an inpatient gynecologic population of 8,463 patients and outpatient visitations of 25,200, 16 neoplastic lesions of the vulva have been seen in our surgical pathology laboratory. In this group there were 4 primary carcinomas, 3 myxofibromas, 3 condylomata acuminata, and one hidradenoma.

The case of hidradenoma is of interest because of the apparently low incidence of this tumor in the non-white population. The case to be reported in detail elsewhere is of a 52-year-old Negro woman seen in 1951 as an outpatient with an asymptomatic calcified nodule of the left labium majus. The nodule was biopsied and measured 0.6 by 0.8 cm. The microscopic sections showed a thick stratified squamous epithelium with the basilar layers containing large melanin deposits. In the corium were hair shafts and sweat and sebacous glands. At one level there was a cystic area lined by columnar epithelium with papilliform projections of single and double layers of columnar cells, and a fine layer of

spindle cells interlacing between the layers of the papilliform projections. The lesion fits all of Novak's, Pick's, and the authors' criteria of hidradenoma. The simple excision apparently was adequate therapy.

The histogenesis and histological characteristics of the tumor have interested us for a long time. When reviewing sweat glands and sweat-gland tumors at the Armed Forces Institute of Pathology I have noted two points of histologic importance in regard to apocrine glands. First, the gland is a single, coiled, tubular gland divided into two portions: a narrow unbranched tube which is purely for excretory purposes and a lower portion which is secretory, and is composed of a thick basement membrane inside of which the spindle or myoepithelial cells lie. The glandular cells in the normal gland rest on the myoepithelial elements in a single layer. In the postovulatory phase of the menstrual cycle there is a tremendous increase in the glandular epithelial cells; indeed, in some instances the glands, particularly in the axilla, become papilliferous in character. I have not personally investigated in detail the perianal or vulvar sweat glands for these cyclic effects in human beings.

A second point of importance is that extreme pleomorphism and metaplastic changes occur frequently in infected secretory glands. It is interesting to speculate that the etiological factors may be a mature gland, infection, and an unusual or atypical target organ response to endogenous estrogen stimulus. The diagnostic criteria of benign hidradenoma as outlined by the essayists are extremely important for certainly it is true that cellular metamorphosis and anomalies of chromatin distribution do not suffice to make a diagnosis of malignancy unless there is invasive growth. This is unfortunate because the absence of invasion is by no means a guarantee against a subsequent malignant clinical course after a local removal.

DR. GREENE (Closing).—We have not considered infection of any particular significance. Six of the 9 patients had inflammatory reactions in the tissues.

The diagnosis of hydradenoma is not as simple as it may have seemed this evening. I was responsible for the diagnosis in most of these cases. At least in one and perhaps in another, I had certain reservations as to whether it was an adenocarcinoma. General pathologists have occasionally called them adenocarcinomas of the vulva. Our treatment was simple excision, and since after two or three years they have shown no recurrence, we think they are simple hidradenomas.

LOCAL HYDROCORTISONE THERAPY OF VAGINAL AND VULVAL PRURITUS

RITA S. FINKLER, M.D.,* NEWARK, N. J.

ALTHOUGH vulval or vaginal pruritus in women occurs frequently if not invariably as only one aspect of a more profound pathological condition, nevertheless the very diversity of conditions, including many with emotional components,[1] that may give rise to pruritus justifies efforts to treat it at least temporarily and provisionally as an entity apart from its underlying cause.

Such symptomatic treatment may be of lasting benefit if the underlying disorder is itself transient, or if suitable therapy can be directed simultaneously against it.

Since it has become known that glucocorticoids, especially hydrocortisone, are effective at the tissue level in suppressing the inflammatory reaction and associated pruritus in various skin disorders,[2-7] these substances have been employed in relieving the intense genital pruritus in women suffering from contact dermatitis or neurodermatitis of the vulva,[8] and atrophic, monilial, trichomonal, and exudative vaginitis.[9-11]

The study to be reported here attempts to evaluate the effectiveness of locally applied hydrocortisone† against vulval and vaginal pruritus due to a variety of disorders.

Materials and Methods

An investigation was made on the effect of locally applied hydrocortisone on genital pruritus in 40 consecutive female patients seen in office practice. The complaint of pruritus was associated with a heterogeneous group of disorders, as shown in Table I, but the hydrocortisone was used primarily in an attempt to alleviate the pruritus, and the results were evaluated accordingly.

The patients were all adult women ranging in age from 17 to 74, with a median age of 47. In most cases there was a substantial history of previous and largely unsuccessful therapy directed toward relief of the pruritus.

When it was determined to employ local steroid therapy, vaginal tablets containing 10 mg. of hydrocortisone free alcohol in a Carbowax base were given to the patient with instructions to insert a tablet deep into the vagina once daily. In more severe cases, one tablet twice daily was prescribed for the first 2 or 3 days, after which the dosage was reduced if possible.

The results of this therapy were evaluated as excellent, good, fair, or poor, taking into account comments of the patient as well as the objective signs of genital and perineal inflammation.

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†The hydrocortisone used in this study was supplied as Cortril Vaginal Tablets by Dr. M. William Amster, Medical Department, Pfizer Laboratories, Brooklyn, N. Y.

Results

A summary evaluation of the therapeutic results is shown in Table I, where it is seen that, regardles of the primary disorder, hydrocortisone was effective in approximately equal proportions of cases. In several patients a vaginal discharge was associated with the pruritus; this was equally responsive to hydrocortisone.

TABLE I. RESULTS WITH LOCAL HYDROCORTISONE IN GENITAL PRURITUS

ASSOCIATED DISORDER	TOTAL	EXCELLENT	GOOD	FAIR	POOR	MEAN LENGTH OF THERAPY (DAYS)
Allergy	6	1	4	–	1	9
Anxiety	5	1	3	1	–	22
Neurodermatitis	5	1	4	–	–	19
Diabetes	3	1	–	1	1	8
Trichomoniasis	3	1	2	–	–	13
Fungal infection	2	1	1	–	–	28
Vulvovaginitis	2	1	–	–	1	20
Pityriasis rosea	1	–	–	–	1	10
Endometriosis	1	–	1	–	–	60
Thyroidectomy	1	–	1	–	–	10
None (essential pruritus)	11	2	6	1	2	9
Total	40	9	22	3	6	
Per Cent		22.5	55.0	7.5	15.0	

In over 77 per cent of the 40 patients, pruritus was practically eliminated, while in an additional 7 per cent some degree of benefit was ultimately achieved.

Undesirable effects of hydrocortisone in this series of cases were remarkable by their absence. In no case was there any evidence of systemic absorption with its attendant complications, nor was there at any time any sign of local irritation due to the hydrocortisone or its vehicle.

Relief of pruritus usually occurred dramatically within the first 24 hours of treatment; it is noteworthy that while the duration of therapy in half the patients was 10 days or less, there was no return of pruritus when hydrocortisone was discontinued except in 3 instances, in each of which the patient had been treated for 10 days or longer.

Hydrocortisone therapy appeared to be equally effective in all age groups studied here; neither the onset of the menopause nor senile atrophic changes in the genitals were correlated with detectable differences in response, nor was any other factor detected in this group of patients that could be correlated with the success or failure of therapy.

Conclusions and Summary

In treating symptomatically a condition which can be due to a variety of causes, highly variable results may usually be anticipated. In this series of cases, however, a remarkably consistent therapeutic effect was achieved in all types of disorders that were treated, considering the relatively small numbers of patients in each category. No substantial differences in effectiveness could be distinguished in the treatment of pruritus associated with various underlying disorders. Instead, the distribution of results in each category was consistent with the over-all distribution of results, where hydrocortisone was effective in relieving pruritus in 85 per cent of these patients.

The diversity of the underlying disorders presented here emphasizes the fact that what has been achieved in this study was only symptomatic relief of pruritus; lasting results must depend on therapy directed toward the primary disorder. The inadequacy of hydrocortisone alone in this regard is indicated by the several instances in this series in which pruritus returned following its withdrawal.

While the complete absence of local irritation and systemic side effects attests the safety of the preparation used, and while it is true that in this study hydrocortisone was used in several patients for periods exceeding 2 months without demonstrable adverse effect, nevertheless it is urged that its use be restricted to short-term therapy in most cases.

It may be concluded from this trial of vaginal tablets of hydrocortisone in 40 patients that this therapy is a safe and uniformly effective method of relieving genital pruritus in women; when it is combined with therapy effective against the underlying cause of the disorder it can achieve complete and lasting relief within 24 hours in most cases.

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MAINTENANCE OF TRICHOMONAS VAGINALIS IN SIMPLIFIED TRYPTICASE SERUM MEDIUM WITHOUT MALTOSE*

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THE occurrence of *Trichomonas vaginalis* infections in female patients of various age groups has been noted in recent studies.[1, 2] Of particular interest is the presence of this flagellate in the very young and in women well past the menopause. In these cases the estrogen effect is wanting and the glycogen deposition in the epithelium is absent or minimal in amount. It appears therefore that *Trichomonas vaginalis* is able to survive in a vaginal environment lacking in epithelial glycogen.

The purpose of this paper is to report an in vitro test of this premise—the cultivation of *Trichomonas vaginalis* in simplified trypticase serum medium without the addition of a carbohydrate.

Materials and Methods

The organisms used in the present experiments were isolated in bacteria-free cultures from the vaginal discharges of 2 white female patients aged 74 years. The natural menopause had occurred 20 and 23 years previously. Both patients exhibited the clinical manifestations of severe vaginitis as the result of local atrophic changes and the presence of *Trichomonas vaginalis.*

The two strains of flagellates were isolated and propagated in the medium of Kupferberg, Johnson, and Sprince.[3] Maltose was not added, however, resulting in the following composition per 800 ml. of final medium: Bacto agar 1 Gm. (dissolved in 400 ml. of distilled water by heating in the autoclave at 10 pounds for 10 minutes); trypticase (BBL), 20 Gm.; cysteine hydrochloride, 1.5 Gm.; and 0.48 ml. of methylene blue (0.5 per cent); adjusted to pH 6.0 with 5 N sodium hydroxide and made up to volume with distilled water. This stock solution was conveniently tubed in 8.5 ml. portions and sterilized. To each stoppered tube, upon cooling, was added 0.5 ml. sterile human serum (100 per cent) which had been adjusted to pH 6.0. The medium was kept at room temperature and used for 4 to 6 weeks.

During the initial transfers the cultures were rendered free of bacteria by the use of 500 units of penicillin and 1 mg. of streptomycin per milliliter of medium. After 6 successive transfers at 72 hour intervals the strains were carried without accompanying bacteria in the modified simplified trypticase serum medium without antibiotics. The two bacteria-free strains of *Trichomonas vaginalis* were maintained serially at 37° C., by weekly transfers of 1 ml. of inoculum obtained from the bottom of the culture tube after slight agitation with the tip of the pipette. Growth was measured by hemocytometer cell counts at irregular time intervals throughout the period of observation.

*Presented at the Symposium sur les infections à Trichomonas, Reims, France, May 28 to 30, 1957.

Results

Strains I and II of the organism survived for 3 months and 20 months, respectively. Over 80 serial transfers of Strain II were made and sustained growth was well maintained through successive weekly subcultures. Strain I had been maintained for 3 months when it died out. The subcultures remained viable for periods of 2 to 4 weeks so that weekly transfers proved to be well within safe limits. In the course of the experiments, however, *Trichomonas vaginalis* Strain II became recontaminated with a hemolytic strain of *Micrococcus pyogenes* var. *aureus*. Nevertheless, the flagellate and bacterium together survived for the total duration of the experiment, a period of approximately 1 year.

Count samplings taken throughout the period of observation did not exceed concentrations of 70,000 flagellates per milliliter, following 72 hours of incubation at 37° C. At times the organism count was found as low as 7,300 per milliliter. The average population of the subcultures totaled 52,500 organisms per milliliter, reached in less than 72 hours.

Comment

These figures are not intended to convey accuracy of count nor are they important as results of the present studies. Their significance lies in the fact that sustained growth of *Trichomonas vaginalis* was maintained in simplified trypticase serum medium without maltose for 20 months. Although growth measured by the number of cells per milliliter was markedly less than in media supplemented by maltose,[4] sufficient amounts of a carbohydrate are present in human serum for the metabolic requirements of the flagellate. Such an observation contributes to an understanding of how the infection may maintain itself in the very young and old female patients. The glycogen of the vaginal epithelium, formed as a result of estrogen stimulation, apparently is not necessary for the survival of this organism in the vagina.

Another important feature revealed by the present study is that *Trichomonas vaginalis* will establish a biologic balance with a bacterium so that growth can be continued for months through a series of subcultures. Although bacteria are not essential to the growth of the protozoon, the possibility that *Micrococcus pyogenes* var. *aureus* provides nutritional stimulation for the trichomonads is not excluded. Pray[5] reported that the life of this flagellate was prolonged when grown with the above bacterium.

Recent work has shown an interest in the maintenance of stock strains with the least expenditure of time and material. McEntegart[6] has shown the practical application of freezing in the maintenance of stock strains of the trichomonads. Local strains of *Trichomonas vaginalis* have been conserved in the presence of *Candida albicans*[7, 8] or *Escherichia coli*,[8] with resulting lower costs of material involved and lesser frequency of transfers. The present study has also demonstrated a method for the conservation of *Trichomonas vaginalis*. The simplified trypticase serum medium without maltose may be prepared in bulk and employed for 4 to 6 weeks when kept at room temperature. Furthermore, the adopted system of weekly transfers at 37° C. proved to be within the safe limits of viability.

Summary

These data show that *Trichomonas vaginalis* will survive and grow in simplified trypticase serum medium without maltose. This experimental evidence supports the clinical observation of the survival of this flagellate in a

vaginal environment lacking in epithelial glycogen. The metabolic requirements of the organism are met by the presence of serum and the nutritional stimulation of bacteria. The resulting metabolism and rate of division of *Trichomonas vaginalis* in this medium afford a method of conserving the flagellates with a minium expenditure of material and time.

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GRANULAR-CELL MYOBLASTOMA OF THE VULVA

LAWRENCE B. WINKELSTEIN, M.D., AND
STANLEY FRIEDMAN, M.D., MOUNT VERNON, N. Y.

GRANULAR-CELL myoblastoma of the vulva is considered an uncommon lesion. Only 20 cases have been reported, but 17 of these have occurred in the last 10 years. This suggests that this tumor has probably been overlooked in the past, and may not be as rare as the paucity of reported cases indicates. For a complete review of the literature and a discussion of vulvar myoblastoma, the reader is referred to a recent article by Chiodi and associates.[1] The purpose of this paper is to present another case.

C. P., a 50-year-old white woman, para i gravida v, was seen in July, 1957, because of a lump on the vulva. She had been aware of this lesion for 18 months, but in the past 6 months it had been growing larger. Her past history was normal and she was 4 years postmenopausal.

Examination of the vulva showed a firm, slightly tender nodule in the right labium majus, measuring 3 by 2.5 cm. The overlying skin had a small, superficial ulceration and was adherent to the nodule. The nodule itself was freely movable. There were no palpable inguinal glands or other abnormalities.

Under local anesthesia, the nodule was excised with a generous amount of the surrounding tissue. The wound healed well.

Pathologic Examination.—The gross specimen consisted of skin and a firm tumor mass. The tumor measured 3 by 2 cm. On section, it showed a smooth, gray-tan surface, and was not encapsulated. Microscopically, the tumor was made up of groups of cells with a granular cytoplasm, separated by strands of fibrous tissue. The cell borders were distinct in some places, indistinct in others. The nuclei showed moderate variations in size and shape and occasional hyperchromatism. The tumor blended into the surrounding tissue. The overlying squamous epithelium showed a marked tendency to growth downward into the stroma and basal-cell hyperplasia (Figs. 1 and 2). The pathologic diagnosis was granular-cell myoblastoma of the vulva and pseudoepitheliomatous hyperplasia of the epithelium.

Myoblastoma is an uncommon tumor in any part of the body. Its most frequent sites are the skin, subcutaneous tissues, tongue, breast, and respiratory tract. A tendency toward multiple sites in the same patient has been noted.

It was first suggested that this tumor was derived from heterotopic rests of embryonal striated muscle.[2, 3] More recently, evidence has been mounting that it is actually of peripheral nerve-cell origin, and the term "granular-cell neurofibroma" has been proposed.[4] The number of malignant myoblastomas reported is very small, making up less than 3 per cent of the total number of cases. All of the vulvar growths have been benign and wide local excision has been curative for these.

We wish to thank Mr. E. Entin for the photomicrographs.

Fig. 1.

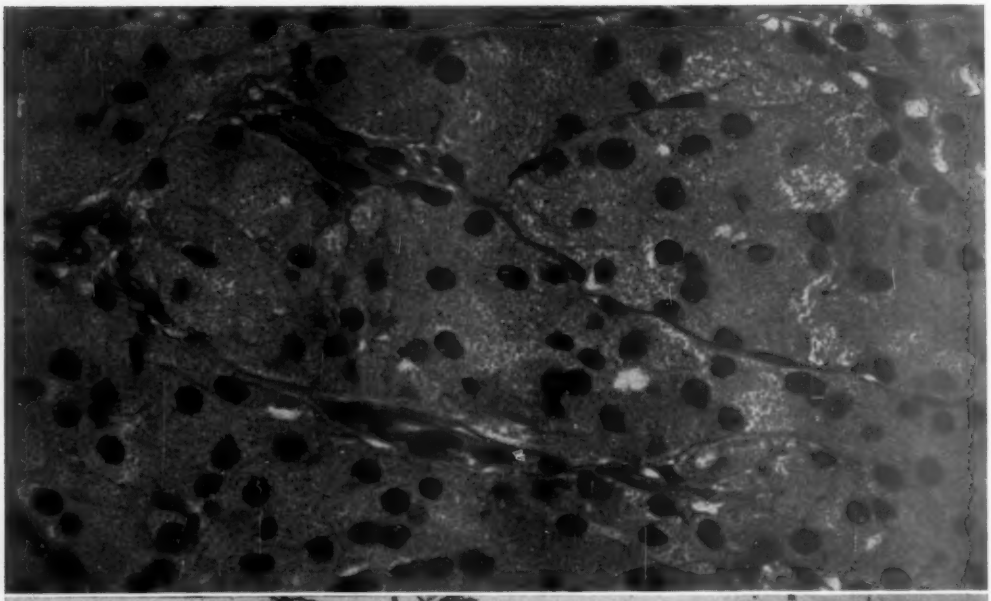

Fig. 2.

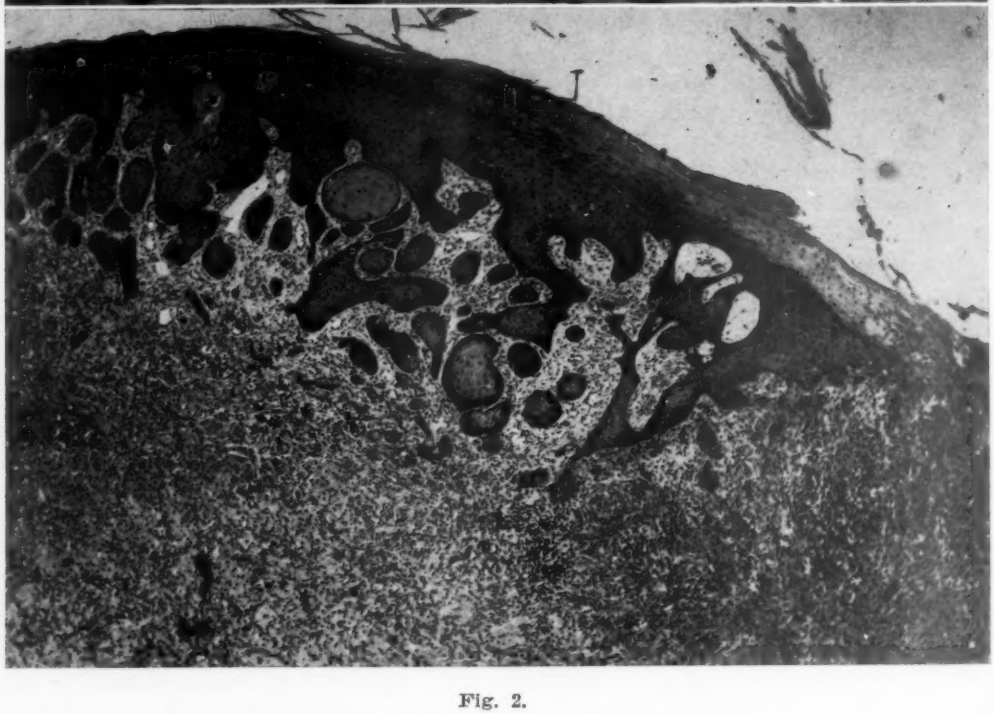

Fig. 1.—Characteristic granular cells. (×650; reduced ¼.)
Fig. 2.—Vulvar epithelium showing downward growth and hyperplasia. (×55; reduced ¼.)

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RADIATION HAZARDS IN OBSTETRICS AND GYNECOLOGY

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TODAY, mainly as a direct result of articles appearing in some of the popular women's journals, there is an ever-increasing number of patients aware of the possible hazards associated with the use of ionizing rays in their various forms. Unfortunately, the scientific journals to which we normally are exposed do little to help us gain some clear conception of the actual extent of these radiation hazards. We are confused in our own minds, and because of this confusion, can do little to alleviate the fears of our patients.

Tangible information is difficult to obtain from our colleagues, the radiologists. They, by and large, are divided into two classes: one class that knows little about these radiation hazards and the physics of radiology in general, and the second class that knows so much about both that they find it difficult to translate their knowledge into a language that we, as obstetricians and gynecologists, can comprehend.

This is an attempt to appraise some of the more important contributions in the recent literature and to interpret them in such a way as to have some meaning for us. I would like to emphasize that I am not a radiologist or a physicist, or indeed a geneticist, but radiologists and physicists who have read this report have not been able to quarrel violently with its conclusions. One should also bear in mind that these articles are based on concepts and information as they exist today. Further investigation and research will undoubtedly call for a revision of our ideas from time to time. The only original work in this presentation includes some verification of dosage schedules that have been reported.

There was noted in this study a marked paucity of information to be obtained from periodicals produced in this country. A great deal of investigation has, however, been done and many fine articles have been written in British and Australian journals relating to the dangers of ionizing radiations. Another interesting observation made was that different investigators could come to diametrically opposed conclusions based on practically identical premises. This paradox seemed particularly common among the geneticists.

Primarily we are concerned with two effects of ionizing radiations, first, whole body or somatic effect and, second, the effect of radiations on the gonads and the consequent effect on heredity.

We are all, and we have been since the birth of the universe, subjected to radiations from naturally occurring sources. This constitutes our original

background radiation and comes from radium and uranium and from radon disintegration products in our environment, from cosmic rays, and from our own body potassium and carbon[14]. This all totals to about 0.1 r a year or about 3 r during the 30 or so years when we are considered to be genetically alive. This, of course, varies considerably from place to place. In the United States it is considered to average about 5 r and in very high altitudes, due to an increase in cosmic rays, may run up to as high as 15 r.

Civilization has added considerably to this background radiation—television, luminous dials on watches, etc., have added negligible amounts. Industry is adding more, particularly to certain people directly associated with facets of these industries. We are all aware of the uses of radioactive isotopes in investigative and therapeutic medicine. We are less aware of their uses in industry. Ionizing radiations are used to detect flaws in steel, to measure with accuracy shapes and sizes of ball bearings, thicknesses of materials, to de-electrify plastic materials and make them more workable, and in ever-increasing amounts to produce power. The horizons for the use of radioactive substances are limitless and hundreds of new uses are found for them yearly. As these horizons are pushed back, so, if we are not careful, will our background of radiation be inevitably increased. The chief therapist at our Cancer Clinic not long ago encountered a patient with leukemia. This man's job had been for years x-raying boxes of chocolates to ensure that they were accurately packed. He encountered also, not very long ago, a patient who complained of chronic nausea, whose job was associated with the oil pipe industry, x-raying pipe unions to ensure accuracy of fit. These are probably not isolated incidents of overradiation attributable to industry.

Again, in addition to our original background radiation, we have the radiations associated with atomic bomb fallouts. These are, at the present rate of testing and with present-day explosives, probably contributing somewhere in the nature of about 0.1 r by the thirty-fifth year of life. A recent visitor from England suggested that the dosage of such fallouts to the gonads is equivalent to a person's wearing two luminous-dialed wrist watches and with his hands constantly in his pockets.

At the present time it is estimated that diagnostic x-rays are increasing our average background dosage by about 22 per cent, that is, by something in the nature of 1 to 2 r in the first 35 years of life. In some areas of Europe and the United States, this increase is in the neighborhood of 100 per cent.

With this introduction, it would be well to discuss gamma radiations and their effects in so far as they involve us as obstetricians and gynecologists, their dangers, and how these dangers can be minimized.

There is irrefutable evidence to indicate that radiation in therapeutic doses to a fetus in the first trimester of pregnancy will cause fetal death or fetal malformations. As the fetal nerve cells are particularly susceptible to the effects of such radiations, the anomalies most frequently encountered will involve the central nervous system, giving microcephaly, cerebral atrophy, idiocy, anomalies

of the eyes, etc. Circumstances under which such radiation would be given are rare but, if they should be present, they constitute ample ground for the interruption of a pregnancy.

There is ample evidence to indicate that gamma rays are carcinogenic. It is a well-known fact that radiologists, and particularly radiologists who make use of radium, are about ten times as likely to develop leukemia as is the general population. We also know that those patients who have been subjected to radiotherapy for ankylosing spondylitis are about ten times as likely to develop leukemia as those who have not been subjected to such therapy. In recent years instances of malignancy of the thyroid and of leukemia are being reported in patients in whom, 5 to 20 or so years ago, as infants, the thymus was x-rayed because of supposed or real enlargement at birth. Radioactive iodine only last year celebrated its tenth anniversary and already some of the thyroids so treated 5 to 10 years ago have been found to show bizarre histological patterns which, although not yet definitely malignant, appear to be closely akin. In a symposium on radioactive iodine in *The Journal of the American Medical Association* last year, it was suggested that the maximum carcinogenic effect would not be apparent until at least 20 years after the original therapeutic dose was given.

In the past year Stewart in England has produced figures that purport to show that if a pregnant woman has a series of x-rays to the abdomen or pelvis, her child will be twice as likely to develop leukemia or some type of juvenile cancer as the child born of a woman not so x-rayed. This would, of course, be of tremendous interest and importance to us if Stewart's conclusions are proved to be correct. It is difficult, however, to believe that such a cause-and-effect relationship has been truly established.

The skin radiation received by the body with the common x-rays that we might use during pregnancy is approximately as follows: This is with a 75 kv. and a 5 ma. machine for fluoroscopy, and approximately 100 ma. for spot films. Bear in mind that the fetus would receive considerably less but in some of these films it would be totally x-rayed.

Chest	0.05 r
Fluoroscopy	0.7 to 1.2 r
Lumbar spine	
Anteroposterior	1.5 r
Lateral	5.7 r
Pregnancy	
Anteroposterior	3.6 r
Lateral	9.0 r
Gastrointestinal series per film	0.65 r
Fluoroscopy	0.28 r per second
Gastrointestinal series with good fluoroscopy	20 to 40 r

Comparing these figures with the dosage schedules operative in an adult who develops leukemia as a result of x-radiation, it seems highly improbable that the x-rays of the mother could possibly influence the development of this disease in the mother or offspring.

Possibly the most controversial of the effects of ionizing radiations are their effects on heredity.

Genes are present in all the body cells and there is irrefutable evidence to indicate that radiation causes gene mutation. Such mutations are of significance, however, only when they involve the reproductive cells. A certain amount of mutation has always been taking place, particularly as a result of our background radiation but any additional source of radiation will increase the chance for additional mutations. It is estimated that there are about 10,000 genes in our chromosomes and constantly about 8 of these are mutant genes. Mutant genes are generally recessive so that for maximal effect they would have to be present in both parents, but recessive genes can be, of course, transmitted from generation to generation and remain dormant. These almost always lead to some harmful effect so that the offspring inheriting the new characteristics may die, or be unable to reproduce, or have some defect that may shorten its life and certainly reduce its fertility. The more harmful the mutant, the sooner it dies out, particularly when medical science does not interfere and salvage those afflicted. There is, however, a tendency for modern medicine to salvage many of these handicapped persons and to retard their natural extinction. An excellent example of this is in diabetes mellitus. Prior to 1926 and the introduction of insulin, diabetic individuals died in infancy or in early life, or were unable to reproduce, and if they did often died during pregnancy. At the present time most diabetic persons live to their reproductive ages and are able to reproduce and, as a consequence, a disease which normally would become nearly extinct in one generation is being handed down from generation to generation.

Geneticists appear to agree that, although certain levels of exposure to radiation are alarmingly dangerous, there is no such thing as a safe level because the rate of mutation varies directly as the amount of radiation received by the gonads and any amount of radiation increases the mutation rate to some extent. Mutation, with few exceptions as noted above, tends to reduce the survival rate of the species, that is, there may be some good mutations but, on the whole, most of them are bad. A species with a few individuals that have some special advantage and that can reproduce enough offspring to replace in a short time a large number of misfits would be able to tolerate a higher mutation rate than one with individuals that have a more limited reproductive capacity. In man it appears that the spontaneous mutation rate is already as high as his reproductive capacity can tolerate or even higher, and again, as noted above, this is particularly true now since medical interference has undoubtedly altered this equilibrium.

What could be considered from a geneticist's standpoint an alarming dose of x-ray? Mutants appear and disappear at the rate of about 0.2 per generation, that is, it would take about forty generations for a mutation to die out, and these mutations are being reintroduced at about the same rate. Geneticists feel that, when a sufficient quantity of radiation is given to double this mutation rate, then this dosage is alarming. What, however, is not universally accepted is the constitution of this so-called doubling dose of radiation in man.

Figures vary from 10 to 400 r to the gonads and the most acceptable figure appears to be in the nature of about 80 r. And just what effect does doubling the mutation rate have? This depends, and this should be stressed, on whether the doubling rate affects a small group or whether, as a result of massive radiation, the whole population is involved. That is, the effect of 80 r on 10 per cent of the population would be, in the long run, the same as 8.0 roentgens on 100 per cent of the population. If a doubling dose were given to the whole population, the result would be that in the first generation the individual would have 8.2 mutants, not 16, as we are doubling the mutation rate and not the number of mutants. It would mean that 1 in 200 would suffer a genetic death in the next generation. Not too many you might say, but it would be 750,000 in a population of 150,000,000, and some 30,000,000 in the next generation out of 150,000,000 would have some detrimental genes that would survive and reproduce. In many generations, say forty, there would be 16 detrimental genes instead of 8, and up to two-fifths of all conceptions would end in loss of reproductive capacity and a large number of survivors would be severely handicapped. This is the long-term effect of doubling the mutation rate and could mean the extinction of the human race.

It has been shown that, from conception to the end of our reproductive years, we have a background radiation dosage of upward of 4 or 5 r, and it has also been suggested that any dosage of radiation to the gonads increases our mutation rate, and that this increase will be alarming with dosages in the nature of 80 r. How nearly do we approach these figures by diagnostic x-ray in women in common use in obstetrics and gynecology:

Chest	0.07 milliroentgens
Lumbar spine	669 milliroentgens
Intravenous pyelogram	1,290 milliroentgens
Gastrointestinal series per film	9 milliroentgens
Barium enema per film	20 milliroentgens
Abdomen	200 milliroentgens
Pregnancy pelvimetry	669 milliroentgens excluding the Thoms inlet picture
Salpingogram	Up to 24,200 milliroentgens
X-ray therapy to the ovaries for the treatment of infertility	80 to 300 r
Whole fetus in pelvimetry	About 2 to 2.5 r

The Thoms inlet gives 2.5 r to the gonads, both fetal and maternal, and this is about 4 to 5 times that of all other fields combined.

It is thus obvious that, although every x-ray that we take and every milliroentgen of x-ray that a patient is exposed to increase the mutation rate, only in therapy directed at the ovaries for sterility do we get what approaches a doubling dose in humans. If, however, the results of Kaplan, etc., are as good as they are reputed to be, it is difficult to see how one can condemn even this procedure in properly selected cases.

We must, however, and can quite easily, take certain steps that will, to a considerable extent, reduce or eliminate unnecessary radiation, both somatic and to the gonads. These may be briefly noted as follows:

There are many variable factors in taking x-rays. There is the skin-tube distance, the voltage and amperage of the machine, the filtration, and the size of the field irradiated. It would appear that skin-tube distance is of little significance. With higher kilovoltage machines, it is true that we reduce the time of exposure, but this is compensated for by an increase in the intensity during the time of exposure so that little is gained. Filtration will affect the surface dosage but has little effect on the depth dosage. We can, however, reduce exposure to the gonads by reducing the size of the field irradiated and by shielding the gonads.

X-rays, particularly to the pelvic organs, should be used only on a definite indication in women until the end of their reproductive years. The same holds true in the use of radioactive isotopes for such conditions as hyperthyroidism. In pregnancy, one should bear in mind the fact that we are radiating both the fetus and the mother and our indications for x-ray must be even more stringent, particularly in the earlier months of pregnancy. In pregnancy it is suggested that exposures for disproportion be taken only with an indication and at a time when the most value can be obtained from such pictures which, as a rule, means during labor. It is felt that the Thoms inlet picture should be discarded because of the excessive exposure to both mother and child and because it is the least valuable of the various films taken for disproportion. I think, in addition, some consideration should be given to discarding the outlet pictures. The most valuable plate is undoubtedly the standing lateral and usually in such a picture the gonads of the fetus will receive only scattered radiation except in the case of a breech presentation. Films should not be repeated because they are not quite perfect. If the information desired can be obtained from an imperfect plate, that plate should be accepted. Consideration should be given to the elimination of x-rays in the diagnosis of placenta previa. Are cystograms and placentograms really necessary? The diagnosis is almost invariably eventually made by vaginal examination. Last, in gynecology, possibly it would be wise to watch for those neurotic patients who travel from doctor to doctor, getting an x-ray of the stomach and duodenum at each stop.

To recapitulate: It appears that ionizing radiations in therapeutic doses in the early months of pregnancy are grounds for the termination of the pregnancy. It appears that ionizing radiations can obviously be a causative factor in the development of leukemia, but it is extremely doubtful that the dosage that a patient receives from us is likely to contribute to any great extent to this hazard. Any dosage of radiation to the gonads will definitely increase the mutation rate but if the doubling dose is considered to be the dangerous dose, then our contribution again will be very real but small except in the rare case in which radiation is given in the treatment of infertility.

Conclusions

Because of the publicity, particularly in the lay press, there has been much confusion in the public mind, and indeed in our minds, regarding the effects on the human race of exposure to various ionizing rays, particularly gamma rays. On the one hand these rays are valuable diagnostic and therapeutic weapons. On the other hand they have some carcinogenic and detrimental genetic effects. These two aspects of these rays must be seen in their proper perspective. It appears that no woman in her reproductive years, and more particularly no woman who is pregnant, should be x-rayed without a proper indication. It seems equally clear that neither should these rays be withheld in such a woman if a valid indication exists. If she is x-rayed, it should be done at a time when the most information can be obtained from this procedure. When she is x-rayed all adequate precautions should be taken to avoid excessive and unnecessary radiation. We must agree that few of us are much interested in our grandchildren forty generations hence, but after all we do have some responsibility to posterity.

Addendum.—Bewley, writing about maternal and fetal radiation dosage during obstetric radiographic procedures, emphasizes the use of spot films rather than fluoroscopic examinations. He also emphasizes that increased voltage will decrease the general radiation.

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TECHNIQUES OF ABDOMINAL TOTAL HYSTERECTOMY, WITH REPORT OF THREE METHODS USED IN 1,000 CASES

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Methods, 1878-1955

THE modern technique of abdominal total hysterectomy began on Jan. 30, 1878, when Wilhelm Alexander Freund[1] of Breslau, after much study, and dissection of many cadavers, removed the uterus from a patient with "cylinder-carcinoma of the entire endometrium."

He instilled 10 per cent carbolic acid into the uterine cavity, lowered the patient's head, elevated her hips (later known as the Trendelenburg position), and entered the abdomen through a midline incision. A traction suture was placed in the fundus of the uterus, and three sutures of silk were used to ligate each side. One suture "penetrated the tube and ovarian ligament," another "encircled the ovarian and round ligament," and the third was inserted through the vagina by an "elastic trocar needle." The latter was thrust up alongside the cervix, anterior to the uterine vessels, where one end of the silk suture 2½ meters long was drawn into the abdomen. Then the needle was withdrawn into the vagina and reinserted posterior to the uterine vessels. The suture on each side was secured, the uterus and cervix were excised, and the two deep mass ligatures were drawn down through the vagina. The slit in the peritoneum, thus produced, was joined together by sutures. A tampon saturated with 10 per cent carbolic acid was inserted in the funnel between the stumps and withdrawn the following day. In discussing the report of this first case, Olshausen spoke favorably of closure of the peritoneum completely; and Schroeder credited the Lister technique for making the operation possible.

Slight modifications in Freund's operation was suggested, such as incising around the cervix through the vagina before the abdominal procedure. Great interest developed in the operation, but the mortality was high due to peritonitis. Because of the great primary death rate from the abdominal hysterectomy many surgeons continued to press for the use of vaginal hysterectomy for treatment of carcinoma of the cervix, which was the main indication for hysterectomy in those days. By 1890, it was becoming apparent that only 10 to 17 per cent of the patients were free of cancer two years after vaginal hysterectomy. Interest in the abdominal approach, with wider dissections, revived, hastened by the gradual development of aseptic surgery.[2]

In 1889, Stimson[3] of Cornell Medical College made a report of 2 total hysterectomies, in which he had applied ligatures "to the uterine arteries alone beneath the peritoneum," before excising the uterus. This technique was an advance over mass ligature, which had been followed by secondary hemorrhage and delayed healing.

In 1892, W. M. Polk[4] of New York reported the use of Stimson's method in 21 cases, 17 for fibroma and 4 for procidentia. The uterine vessels were ligated by means of an aneurysm needle. The cervix was excised from the vagina by a circular incision, beginning above the bladder reflection, turning down the peritoneum until the vagina was reached. After excision, four catgut sutures were placed at four angles from the vagina up to the peritoneum, anteriorly, posteriorly, and laterally. These were tied individually, then all together, and pulled down through the vagina. The vagina was then packed with gauze, a glass drainage tube was placed from above into the cul-de-sac (for 12 to 24 hours), and the abdomen was closed. Fifteen of the 17 fibroma patients survived with good results.

Radical hysterectomy for carcinoma of the cervix was described simultaneously, in 1895, by Rumpf,[5] and by Ries,[6] in Germany, and by John G. Clark[7] of Philadelphia. Clark ligated the uterine vessels laterally, mobilized the ureters, excised the base of the broad ligaments, left the vagina open, and placed a gauze drain beneath the peritoneum.

In 1898, Werder[8] of Pittsburgh reported an operation directed particularly at removing the vaginal fornices and upper vagina, in a case of carcinoma of the cervix. The exact technique was not stated clearly, particularly as regards protection of the ureters. The short vagina was apparently left open, after being divided by the cautery.

Wertheim,[9] in his technique of radical hysterectomy, divided the uterine vessels after passing the index finger through the canal carrying the ureter. The uterosacral ligaments were incised near the posterior wall of the pelvis. Large right-angle clamps were placed low across the vagina. The cuff was sutured around, and left open. Then the lymph nodes and fatty tissues over the vessels were exised. Removal only of enlarged lymph nodes was considered necessary.

In 1917, Baldwin,[10] of Columbus, Ohio, reported that he had performed 2,018 abdominal hysterectomies by his method. Apparently this is the first report of any large number of total hysterectomies for benign lesions. Tincture of iodine was instilled into the uterus. The ovarian vessels were divided and sutured, the round ligaments incised but not ligated, the uterine vessels cut and ligated. The bladder was mobilized and pushed down on the vagina, and the posterior peritoneum was incised and separated between the uterosacral ligaments. The vagina was then entered anteriorly, and the cervix was excised. With the use of a double strand of No. 1 chromic catgut, each round ligament was sutured into the vagina at the angles, the knot being on the vaginal side. A purse-string suture was passed around the vagina, beneath the round ligaments and without penetrating the mucosa, closing without drainage. The pelvic peritoneum was closed with a continuous suture. In 1929, Nelson[11] stated that the Baldwin method had been used at the Henry Ford Hospital in 476 cases, with 2.9 per cent mortality, and 7 per cent complications. This method continues to have its adherents today.

In 1918 Kelly[12] described, and Brödel illustrated, the radical total hysterectomy for carcinoma of the cervix. He made no mention of total hysterectomy for benign disease of the cervix. Kelly developed many ingenious variations in the technique of subtotal hysterectomy (right-to-left, bisection, etc.). It is interesting that in his method of radical hysterectomy, the bladder peritoneum was sutured to the anterior vaginal wall, and the rectovaginal fold to the posterior vaginal wall. A gauze drain was placed in the pelvis leading out through the open vagina.

In 1920 Polak[13] described total hysterectomy for benign disease. The uterine vessels were clamped and cut, the cervix excised, the vagina closed without drainage, the uterine vessels ligated, the round ligaments drawn to the vagina, and the broad ligaments closed with a continuous suture. No actual case reports were cited.

Masson,[14] in 1927, described his method, in which he clamped and cut the uterine vessels, then excised the cervix, entering the vagina posteriorly. A running mattress suture reinforced with interrupted sutures closed the vagina. The uterine vessels were ligated by a double strand suture, ligaments attached to the vagina, and peritonization accomplished. He felt there was no need for drainage.

In 1928, Graves,[15] of Harvard, advised closure of the vagina without drainage, after removal of the cervix. Sometimes the vagina was closed at the angles, and a subperitoneal drain was placed beneath the closed peritoneum. In the same year Lahey[16] suggested that a shell of cervix should be left after excision, to be closed with mattress sutures (as had Worrall[17] of Sydney in 1917). In the same year, Richardson[18] of Baltimore first presented his technique, particularly describing his angle suture after excision for noncancerous disease. The suture first passed through the anterior vaginal wall into the lumen of the vagina 1 cm. medial to the angle, transfixed the stump of the basal portion of the detached and ligated broad ligament, then passed through the posterior edge of the vagina and the stump of the uterosacral ligament. When tied, this suture closed the lateral vaginal angle. The vagina was further closed completely with figure-of-eight sutures, or a small opening was left for a drain into the abdominal cavity.

In 1929, Richardson[19] further described his technique, illustrated by Brödel, and emphasized the importance of his "T" incision in the pubocervical fascia, to draw the fascia to the angles for strengthened support and to control bleeding from the small vessels in the fascia.

In 1930, Solomons,[20] from the Rotunda Hospital in Dublin, described his technique: the vagina was closed completely with interrupted inverting Lembert sutures, and the peritoneum was approximated with a long, continuous suture across the pelvis. If there had been spill or oozing, a pack of iodoform gauze was left in the parametrium, leading out through the vagina, and the peritoneum was closed over it.

Von Graff,[21] in 1932, reported the use of the "conservative Wertheim operation" in 200 patients, without a death. After division of the ovarian and round ligaments, successive clamps were placed along the uterus, with incision down to the vagina. The cervix was then excised. Bleeding points in the vaginal edge were sutured as necessary, and sutures were placed about the clamps on the broad ligaments. A strip of gauze was introduced into the vagina to provide drainage, and the peritoneum was closed with interrupted sutures. The open vagina was to act as a natural drainage canal for the extraperitonized ligature stumps.

In 1938, Farrar,[22] from the Women's Hospital in New York, presented a detailed discussion of the anatomy and technique of total hysterectomy. She stated that few in America had advocated total hysterectomy for benign diseases of the cervix, while in Europe the supravaginal operation was called the "American operation." In France, Doyen, Wiart, and Forgue, and in Germany and Austria, Bumm, Döderlein, and Weibel, and before the latter, Wertheim, had advocated the total operation for nonmalignant conditions necessitating hysterectomy. In England, Mr. Herbert Spencer practiced total hysterectomy for benign conditions and published statistics of his cases. The higher mortality rate deterred many surgeons from adopting the operation for benign disease.

Farrar believed that all cervical erosions should be treated and encouraged to heal before operation, in order to prevent infection. She injected 3.5 per cent tincture of iodine into the uterine cavity, as a preoperative measure. Packing was inserted in the vagina, and kept in place until 8 hours after the operation. The uterine vessels were ligated without clamping, the uterosacral ligaments were incised and ligated. The fascia was incised completely around the

cervix, above the line where the uterine vessels were ligated. The cardinal ligaments were cut but not sutured. The vagina was opened posteriorly and the cervix excised. The angles were closed as with the Richardson angle suture, except that she also incorporated the round ligaments into the anterior vaginal wall. The middle of the vagina was closed with interrupted sutures, again incorporating the round ligaments. The tubes, uteroovarian and uterosacral ligaments were drawn to the angles, and the bladder peritoneum was attached to the posterior cul-de-sac.

Mohler,[23] in 1945, used no clamps in ligation of the principal vessels. The vagina was closed completely with a continuous suture, inverting the vaginal mucosa into the canal. The ligaments were drawn to the vagina. Allis clamps were used on the vaginal mucosa to reduce crushing of tissue.

Te Linde,[24] in 1946 in his *Operative Gynecology,* described a variation of the Richardson technique, stressing the use of the Richardson "T" in the pubocervical fascia. The cervix was excised after clamps were placed across the vagina beneath the cervix, which often closed the vagina completely, when cut across. The center between the clamps was closed by a figure-of-eight suture, and the lateral angles were closed with a mattress suture beneath the clamps. The ligaments were attached to the vagina. No drainage was used.

Counseller,[25] of the Mayo Clinic closed the vagina by continuous mattress suture, everting the cut edge. The same continuous suture was brought back over the first suture line to reattach the pubocervical fascia. The cardinal ligaments and uterine vessels were ligated by one suture, which also attached them to the vagina. Each round ligament was then attached to the vagina. A running suture closed the peritoneum.

In 1950, Aldrich and Meredith[26] presented their technique, said to be a combination and modification of various steps previously described by Worrall, Richardson, Danforth, Masson, and others. The fascias between the uterosacral ligaments and between the cervix and bladder were separated and held by Allis clamps. After excision, the Richardson angle sutures were inserted. The vault of the vagina was closed with a running suture, then the fascial cuff was sutured over the vault with a running suture, reattaching the uterosacral ligaments. A purse-string suture was used to peritonize each side over the vagina. The proximal ends of the cardinal, round, uteroovarian or infundibulopelvic ligaments were not attached to the vaginal cuff. Significant postoperative complications occurred in 5.7 per cent of 500 cases; but no mention was made of postoperative bleeding.

Burch and Lavely,[27] in 1954, in their splendid monograph, illustrated their method of "posterior three-quarter intrafascial hysterectomy." An important part of the operation is palpation of the ureter with the forefinger in the cul-de-sac and the thumb over the uterine vessels, before placing the uterine clamp in a low position (at or below the level of the uterosacral ligaments). The uterine vessels were cut and ligated singly. The uterosacral ligaments and posterior cervical fascia between these ligments were then cut. The cardinal ligaments were divided and sutured. The pubocervical fascia was not mobilized. The cervix was excised and the vagina sutured around with a continuous suture. Neither the cardinal, round, nor ovarian ligaments were reattached to the vagina. The round and ovarian ligaments were allowed to fall laterally and the peritoneum was closed with a continuous suture. In 837 total hysterectomies, 27.1 per cent showed morbidity (temperature of 100.4° F. on 2 consecutive days after the first postoperative day); less than 1 per cent had significant postoperative bleeding. There were no deaths.

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Left tube, uteroovarian and round ligaments divided and doubly ligated; right round ligament and ovarian ligament ligated and divided; bladder peritoneum mobilized.

Fig. 2.—Uterine vessels isolated, triply clamped, cut, and doubly ligated.

Fig. 3.—Richardson's "T" incision in pubocervical fascia.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Uterosacral ligaments clamped, ligated, and divided.
Fig. 5.—Cardinal ligaments clamped, cut, and ligated, inside the "T."
Fig. 6.—Cervix excised from vagina. One clamp anterior, posterior, and at each lateral angle.

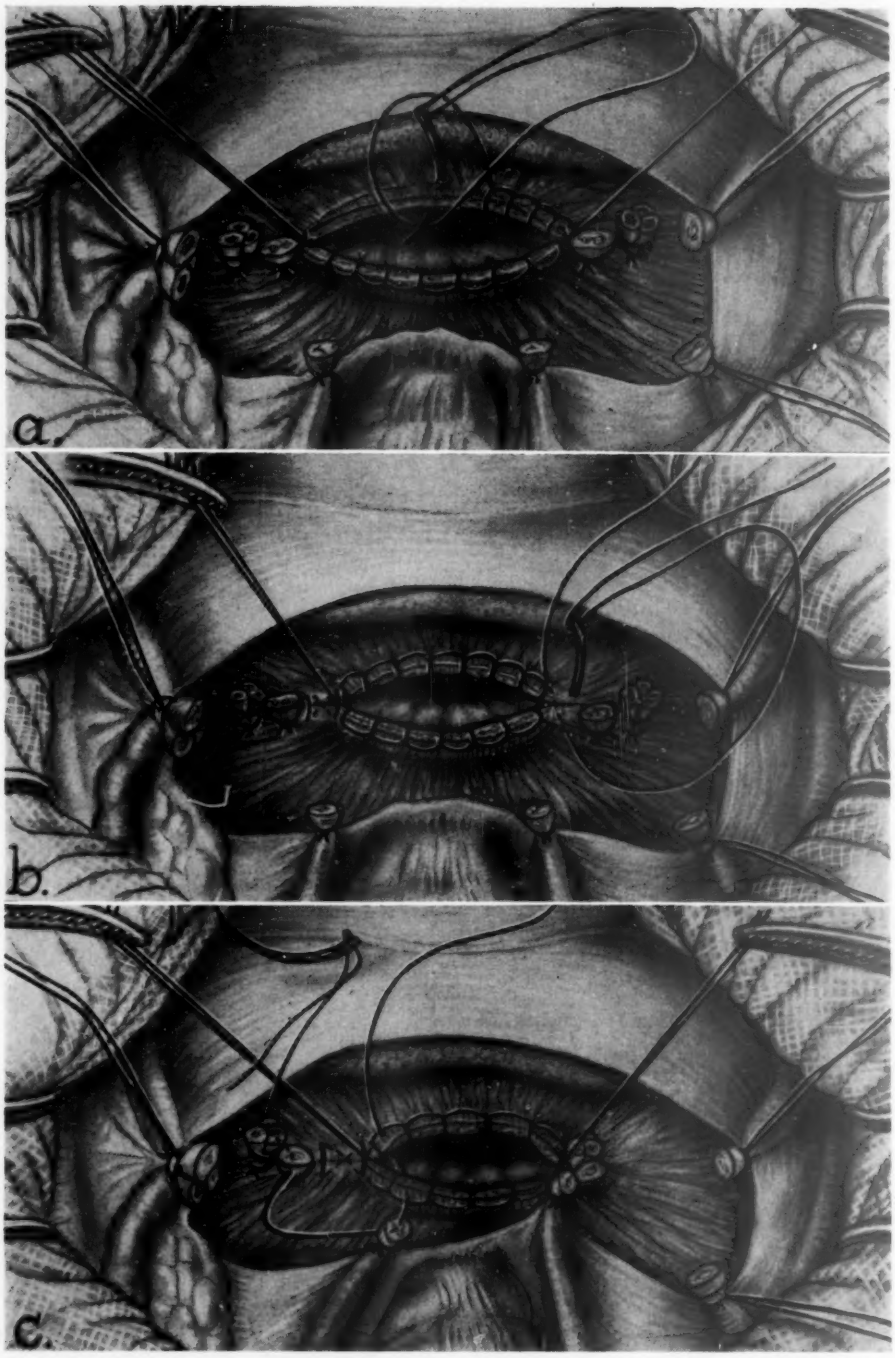

Fig. 7.—*a*, Lock stitch along posterior vaginal cuff, then another along anterior edge.
b, Partial closure of angles with figure-of-eight sutures.
c, Uterosacral and cardinal ligaments sutured to angles.
d, Round ligaments, tubes, and ovarian ligaments attached to angles, reefing the broad ligaments.
e, Bladder peritoneum, round ligament, uterosacral ligaments drawn to posterior vaginal wall.
f, Remaining bladder peritoneum sutured to posterior vaginal wall.

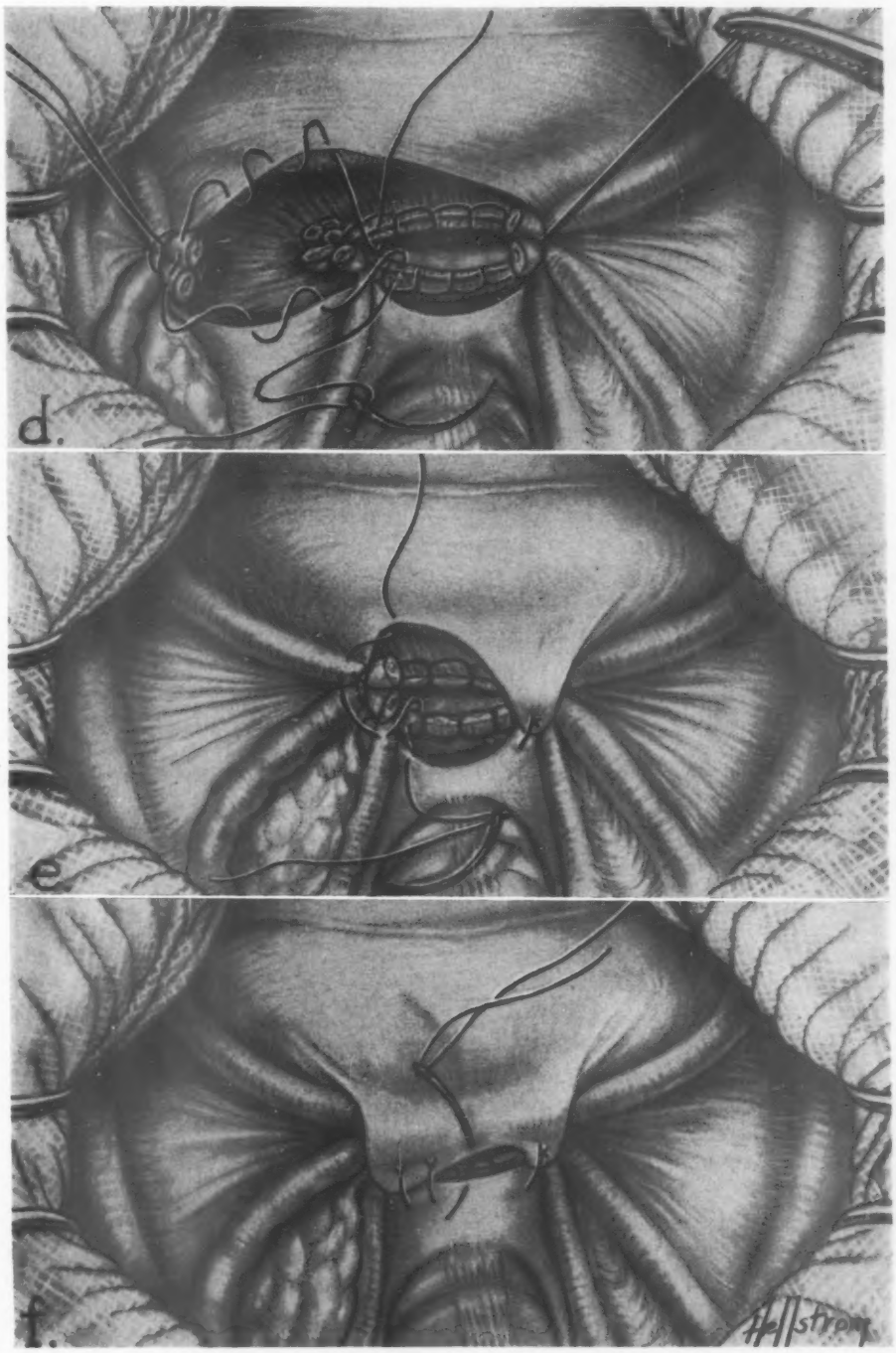

Fig. 7, *d-f.—For legend, see opposite page.*

Methods Used in This Series

In 1937, T. S. Cullen taught me, in the rare total hysterectomy for benign disease, to suture around the vagina with a lock stitch, attach the bladder peritoneum to the anterior vaginal wall, and leave the vagina open into the abdominal cavity, after the Kelly method. Two vaginal cigarette drains were

loosened on the fifth day, and removed on the seventh. Cullen felt that the bladder peritoneum should never be drawn over the open vagina because of the danger of vesical fistula.

Richardson at the same time was teaching his technique, with his special angle sutures, and usually with a small intraperitoneal vaginal cigarette drain. Richardson's unusual operating ability, his insistence on control of all bleeding, and his gentleness with tissues undoubtedly contributed greatly to the success of his carefully designed method.

The Richardson technique, usually with closed vagina and no drainage, was used by us from 1937 to 1949. After two severe late vaginal hemorrhages from the angles of the vagina, extra efforts were made to suture the angles with figure-of-eight sutures beneath the Richardson angle sutures. The occurrence of another hemorrhage after this made me extremely interested in the technique of Falk,[28] described in 1950, in which the vagina was left open. First, he placed a figure-of-eight suture in each angle, attaching the paravaginal tissue. Then a continuous lock stitch was inserted across the posterior edge of the vagina. A separate lock stitch extended across the anterior edge. The round and ovarian ligaments were sutured to the uterosacral ligaments at the angles of the vagina. The bladder peritoneum was sutured to the peritoneum of the posterior cul-de-sac. Falk demonstrated his method in exhibits, and published it only in the *Harlem Hospital Bulletin,* without a report of cases.

In mid-year 1949 our technique was changed, inserting the technique of the open vagina into the Richardson operation. This method comprises the following steps (Figs. 1-7):

a. A midline incision is preferred, transverse occasionally (in the obese).

b. Small vessels in the line of incision are coagulated (mosquito clamps and cutting current for coagulation).

c. The wound is protected thoroughly by skin towels and moist pads.

d. Palpation of the gall bladder, liver, stomach, etc., always precedes pelvic surgery.

e. If the ovaries are to be removed, a Kelly clamp is placed on the infundibulopelvic ligament, two sutures (No. 0 chromic) are applied, the second is transfixed, and the ligament is cut.

f. The round ligament is clamped, looped with a suture, transfixed, and cut. If the ovaries are to be conserved and if the ligaments are closely approximated, the tube, uteroovarian and round ligaments are compressed, a clear space in the broad ligament is incised, and three straight Ochsner clamps are applied. An incision is made between the first and second clamps, and two transfixion sutures are inserted beneath the second and third clamps. If the round ligament is widely separated, it is ligated and divided individually.

g. The bladder peritoneum is mobilized 1 cm. below its attachment to the uterus. (This is usually about 2 cm. above the bladder.) With a sponge stick the bladder is pushed low onto the vagina, and small bleeding points are coagulated. Occasional larger veins are ligated with a No. 3-0 chromic suture.

h. The posterior peritoneum covering the uterine vessels is incised and separated downward, the uterine vessels are exposed with the sponge stick, and three curved Ochsner clamps are applied immediately below the corpus. An incision is made between the first and second clamps, and around the ends of the clamps alongside the cervix, after which the major vessels are ligated twice.

i. The uterosacral ligaments are individually outlined with the curved Ochsner clamps, sutured, and cut. The peritoneum between the uterosacral ligaments is incised and separated from the posterior vagina.

j. The "T" incision of Richardson is made in the pubocervical fascia, the cross of the "T" well up on the cervix near the ligated uterine vessels, the stem of the "T" extending to the level of the tip of the cervix (but not into the bladder, which must be recognized). The flaps under the "T" are mobilized with a scalpel.

k. The cardinal ligaments are clamped with straight Ochsner clamps, inside the reflected "T" anteriorly, and the uterosacral ligament posteriorly, incised, and sutured with a mattress suture. This ligament is again clamped deeper, cut, and sutured as many times as necessary, frequently only once, but at other times several sutures are necessary, especially if the cervix is unusually elongated. Large "bites" are avoided, as they may compress the ureter.

l. After palpation shows that the cardinal ligament has been incised and sutured almost to the level of the tip of the cervix, new packing is inserted to wall off the posterior pelvis. The vagina is opened anteriorly between two Ochsner clamps, cut around the cervix with a scalpel, and an Ochsner clamp is attached at each angle, and on the anterior and posterior walls.

m. A half length No. 0 chromic catgut suture is inserted along the posterior wall as a lock stitch, and secured at the opposite angle. A second lock-stitch suture is inserted in the anterior vaginal wall.

n. The angles of the vagina are narrowed by a single figure-of-eight suture on each side (unless the vaginal opening is quite small).

o. A purse-string suture on each side attaches the uterosacral and cardinal ligaments to the angle of the vagina.

p. A "pulley" angle suture draws the lateral portion of the bladder flap, one round ligament, tube and ovarian ligament, and the posterior sheath of the broad ligament to the vagina. By this means the ovarian and round ligaments are attached to the vagina.

q. The bladder peritoneum is attached to the posterior peritoneum with interrupted sutures, each lateral suture taking a portion of the round ligament proximal to its ligation. This inverts the stump of the tube, uteroovarian and round ligaments. Fine chromic sutures attach the remaining central bladder peritoneum to the peritoneum of the cul-de-sac.

r. The sigmoid is draped over the operative site in the pelvis, the omentum is drawn down, and the abdomen is closed in layers, with a No. 0 chromic catgut suture in the peritoneum, interrupted No. 2-0 silk in the fascia, No. 3-0 chromic catgut in the superficial fascia, and interrupted No. 3-0 silk as end-on-mattress sutures in the skin.

Results in 1,000 Total Hysterectomies

In our series of 1,000 abdominal total hysterectomies (Table I), 15 patients were treated with the Richardson technique, with a *small cigarette drain* extending into the cul-de-sac, which was removed after 48 hours. Anterior and posterior repair was performed in none, and posterior repair alone was performed in one case. Severe postoperative hemorrhage with deep shock occurred in one patient on the seventh day. This was treated by suture through the vagina and multiple transfusions. Another developed a small mass above the apex of the vagina which persisted for 9 months. A third developed a wound infection, attributed to stay sutures. The final results in all were excellent.

In 328 cases (one-third) the Richardson technique with *closed vagina* was used. Anterior and posterior repair was performed in 29 cases, and posterior repair alone in 98 cases. Two patients bled severely, on the fourteenth and twenty-fourth postoperative days. The vagina in each was resutured from below. Multiple transfusions were necessary. Another patient, in whom the cervical stump was removed by means of the same technique, had profuse

bleeding 17 days after operation and required resuturing and multiple transfusions. She was not included in the series although the closed technique was the same. One patient required packing for bleeding. One obese woman with a chronic cough had an evisceration, the incision was resutured, and she developed a ventral hernia. One patient developed a pelvic abscess, one developed phlebitis, 2 had small nonfatal pulmonary emboli, and one had severe cystitis. One patient died, suddenly and unexpectedly, as she was preparing to leave the hospital. The symptoms suggested pulmonary embolus. Autopsy was not obtained. The final clinical and anatomic results in the 327 survivors were quite satisfactory.

TABLE I. COMPLICATIONS AFTER ABDOMINAL TOTAL HYSTERECTOMY IN 1,000 CASES

	VAGINAL DRAIN 15 (1.5%)	CLOSED VAGINA 328 (32.8%)	OPEN VAGINA 657 (65.7%)	TOTAL
Postoperative hemorrhage:				
Sutured	1	2	5	8
Packed	0	1	4	5
Intestinal obstruction	0	0	4	4
Ileus	0	0	5	5
Evisceration	0	1	1	2
Ventral hernia	0	1	0	1
Pelvic abscess	1	1	1	3
Wound infection	1	0	4	5
Wound hematoma	0	0	4	4
Phlebitis	0	1	2	3
Embolus (nonfatal)	0	2	0	2
Pyelitis	0	0	2	2
Cystitis	0	1	1	2
Enteritis	0	0	1	1
Pneumonia	0	0	1	1
Deaths (embolus)	0	1	1	2
Total	3	11	36	50

Our *open technique* has been used in 657 cases (two-thirds) (Figs. 1-7). Anterior and posterior repair was performed in 18 cases, and posterior repair alone in 136 cases. There was postoperative hemorrhage, requiring resuture and transfusions, in 5 patients. One hemorrhage occurred eight hours after operation for removal of a pregnant uterus. This undoubtedly was due to a technical error in the application of the sutures. Another occurred on the tenth day in a patient with severe hypertension, which seemed to be a causative factor. The third occurred 10 days after operation, secondary to necrosis of the vaginal edges, apparently due to subclinical infection. The fourth occurred on the twelfth day, in a patient who had repair of cytocele and rectocele and abdominal total hysterectomy. In this case there was recurrence of the hemorrhage on the eighteenth and twenty-fourth days, each time requiring resuture. Necrosis of the edges of the cuff suggested infection as a cause. Cuture of the vaginal secretions showed *Staphylococcus albus* sensitive to Furadantin. This drug was given. The final result was excellent. The fifth patient bled severely on the twenty-fifth day, and resuturing was done, but bleeding recurred and resuturing was necessary seven times in the next 4 weeks. More than 50 transfusions were given. Friedländer's bacilli were cultured from the vagina, which showed necrosis at the suture lines. Finally, suture with No. 2-0 cotton (removed one year later) was followed by a good result. She developed combined lateral sclerosis, typical of the type associated with pernicious anemia, while under treatment for the bleeding. The diagnosis of pernicious anemia was confirmed by examination of blood and bone marrow smears.

In 4 other patients with moderate bleeding, occurring more than 2 weeks after operation, the vagina with packed with satisfactory results. In the cases in which resuturing was done, packing was inserted, but the separation of the vagina continued to become larger and bleeding continued.

There were a number of other complications in this third group, but these seemed unrelated to the open technique. They included ileus in 5, intestinal obstruction requiring reoperation in 4, phlebitis in 2, hematoma in the abdominal incision in 4, infection of the abdominal incision in 4, pelvic abscess in one. Separation of abdominal wall fascial sutures occurred in one case, on the day of operation, due to severe cough and straining. Pyelitis was marked in 2 cases, and cystitis was severe in one. Enteritis and pneumonia occurred in one case each. One patient died suddenly, on the fourteenth day, apparently from pulmonary embolus.

Comments

First, it becomes evident that there is more than one method of performing total hysterectomy for securing good results. Of the three methods used in this series—the intraperitoneal vaginal drain, the closed vagina, and the open vagina-closed peritoneum techniques—no obvious difference in the final result is apparent. The vagina appears as normal, of the same normal depth, rarely very slightly shortened, with each method. The tissues at the apex of the vagina have seemed thin in occasional cases with each method, probably more so with our open vagina method. The possibility of rupture of the vagina from extremely vigorous sexual intercourse or following extreme intra-abdominal pressure must remain as a possible and rare late complication, but as a rule there has seemed a reasonably thick wall reformed at the apex of the vagina.

There was no real decrease in complications in one method over the other. Many of the complications had no bearing on the technique of closure of the vagina (as abdominal wall hematoma, infection in incision, evisceration, and intestinal obstruction). There was no peritonitis with either method. One patient with an intraperitoneal vaginal drain developed a mass, presumably inflammatory, which was gradually absorbed over a period of months.

Febrile reactions seemed equally low. From 1940 to 1942 sulfanilamide crystals were placed in the closure of each vagina (from 1942-1946 this was continued in a large number of cases at the Walter Reed General Hospital, not included in this series of private cases). From 1946 through 1948 penicillin was given intramuscularly in every case routinely. Since 1949, when our open technique was started, no antibiotic was given, except that all patients who had colporrhaphy procedures were given penicillin-streptomycin intramuscularly for 5 days. The induration in the extensive perineal repair was greatly diminished with the latter therapy, but routine antibiotic therapy in the total hysterectomy without repair has not appeared to be indicated. Increasing use of sulfonamide (Gantrisin) in any patient who has catheterization, or pyuria, or even any bladder symptom, has averted almost all cystitis and pyelitis.

The most common serious complication of abdominal total hysterectomy is postoperative hemorrhage. Severe bleeding occurred in 8 cases (0.8 per cent). In one case, hemorrhage on the day of operation undoubtedly was due to imperfect application of a suture. In the remaining 7, the bleeding was of a different nature, being delayed from the seventh to the twenty-fifth day after operation. The vaginal cuff showed necrosis along the edges, and the bleeding occurred from the small arteries in the vaginal mucosa. It never appeared that the bleeding was from the uterine or ovarian vessels.

Those with a previously closed vagina and subsequent hemorrhage have showed wide separation of the cuff. Many others, with original closure of the vagina, have shown separation of the cuff, on inspection near the fourteenth

day. Some degree of separation seems to be the rule, probably because of slough of normal tissue between the sutures and because of slight subclinical infection in the cuff. At this time, it is improbable that the vagina can be sterilized of bacteria, either at the time of operation or postoperatively. Of the 7 cases of hemorrhage from the eighth to the twenty-third day (one occurred on the day of operation), the following antibiotics were given: Group 1, one case, none; Group 2, 2 cases, of which one had prophylactic penicillin; and Group 3, 4 cases, of which 2 had penicillin-streptomycin intramuscularly twice daily for 5 days, and 2 had no antibiotic. In 4 of the 7 cases of delayed bleeding, there was a delayed temperature elevation to 99.6 to 101° F. from the seventh to the fourteenth day.

Some degree of bleeding from the vagina after operation is the rule after total hysterectomy by any method. Often the bleeding is only a stain, but it may become more obvious near the fourteenth day, at times as much as or more than menstruation. This has continued to occur, even with the open-cuff technique. As a rule, the bleeding is of little consequence, and reassurance suffices. In 5 cases, a pack in the vagina for late and moderate bleeding gave a good result. But the usual bleeding, though infrequently of extreme degree, must indicate dissolving of the sutures, slough from constriction of the vaginal edges by the sutures, and slight infection along the cuff. The sutures must dissolve, slough may be decreased by delicate technique, but some must remain until we learn to make the edges adhere directly together, and the mild subclinical infection must continue until an antibiotic or other technique is devised to eradicate all bacteria from the vagina throughout the postoperative course. Since the vagina tends to slough open, when sutured closed, it seems more logical to leave the vagina open to drain any extravasated blood, serum, and exudate that may form from trauma or infection. In the cases of postoperative hemorrhage with these methods, slough of the vaginal edges has been the rule. Cultures of the vagina were done in 2 cases with recurrent hemorrhages; one showed *Staphlococcus albus,* sensitive to Furadantin, and the other Friedländer's bacillus.

Care of postoperative bleeding has included reassurance for scant bleeding, bed rest for occasional moderate bleeding, packing for very rare late bleeding, and suture of the vaginal cuff through the vagina for hemorrhage. Exposure has been difficult. When the edges were visualized a figure-of-eight suture closed each angle, and usually the anterior and posterior margins were approximated with an interrupted suture. Such complete closure is not truly desirable. In one case a mass appeared in the lower abdomen with fever and pain, gradually subsiding. Six years later salpingo-oophorectomy was necessary for chronic salpingitis; the tubes and ovaries had been normal at the original operation. In 2 other cases, recurrent severe bleeding followed resuturing, due to continued slough. The main problem at the time is to control the hemorrhage. In none was the abdomen reopened, but it is conceivable that this might be necessary.

Granulation tissue at the apex of the vagina occurs with all methods of total hysterectomy, and is variable from case to case. As a rule, it is definitely increased with the open-vagina technique, at times being most exuberant. It is treated by the application of silver nitrate each six weeks, and at times with excision by the biopsy forceps. All patients are followed until complete healing.

It has seemed in recent years, with the open-vagina technique, that temperature elevations have been lessened, especially in the late postoperative period, although exceptions always appear. Leaving the vagina open beneath the closed peritoneum has seemed a better surgical principle, to provide drainage of any accumulation of serum or blood from the extraperitoneal spaces, to hasten drainage of the small subclinical apical abscess that probably forms commonly with the closed technique, and to anticipate an opening that often occurs by slough.

Summary and Conclusions

1. Total abdominal hysterectomy in 1,000 cases was accomplished, with the use of a vaginal drain in 15, closure of the vagina in 328, and the vagina open beneath the closed peritoneum in 657.

2. There were 2 deaths, each apparently from pulmonary embolus.

3. Complications of significant degree occurred in 50 cases (5.0 per cent).

4. Severe vaginal hemorrhage occurred in 8 cases; once in the first, twice in the second, and 5 times in the third group.

5. Other complications included ileus in 6 cases, intestinal obstruction in 4, wound infection in 4, wound hematoma in 4, evisceration in 2, and nonfatal emboli in 2.

6. Good results may be achieved by many techniques. Theoretically, the open-vagina technique has seemed a better surgical principle, to provide extraperitoneal drainage, both immediate and late.

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Obstetrics

THE OUTLOOK FOR FUTURE PREGNANCIES IN WOMEN IMMUNIZED TO Rh*†

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BETWEEN Jan. 1, 1935, and Jan. 1, 1955, 241 women who have been immunized to D (238) or c (3) have given birth at this hospital to 302 erythroblastotic infants or fetuses. These same women have had 18 spontaneous abortions and 9 Rh-negative infants, making a total of 329 pregnancies in which we have observed them. Not included in the figures are women known to be immunized but who in this hospital have had only Rh-negative infants, spontaneous or therapeutic abortions.

We have been anxious to find out what to expect in future pregnancies and what effect the outcome of earlier pregnancies might have on a current pregnancy in order to know what counsel to give our patients concerning future childbearing. We initially analyzed these patients only in relation to the outcome of the first affected pregnancy. It became apparent early in the analysis that the place of the affected child in the total pregnancies of any patient did not alter the conclusions that could be drawn. Consequently, it seemed desirable to divide these patients into three principal groups and to include in one group all the women who have given birth at our hospital to at least one surviving child, in another all women who have had at least one child who died, and in the third all who have had at least one stillbirth. Because of this, 17 women are included in 2 groups and 1 is considered in all 3 groups.

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There were 119 who were delivered in this hospital only of infants who survived, 59 who were delivered only of infants who died, and 49 who were delivered only of stillborn fetuses weighing over 400 grams.* In addition 6 had at least one child who lived and one who died, 7 had at least one who lived and one who was stillborn, 4 had both deaths and stillbirths, and one had at least one pregnancy in each category.

Mothers With Surviving Erythroblastotic Infants

Of the 302 pregnancies in immunized women in which a reportable fetus or infant was delivered, 149 terminated in the birth of a surviving child. These pregnancies were found among 133 patients, 3 having had twins both of whom survived, 11 having had 2 surviving erythroblastotic infants in different pregnancies, and one having had 3 such infants.

Pregnancies Preceding Evidence of Immunization.—There were 20 women who had no living children at the time their first surviving erythroblastotic infant was born. Six of these had had no pregnancies but had received transfusions which were believed to have been the cause of the immunization. Ten women had had a total of 21 unsuccessful pregnancies terminating in 9 neonatal deaths, one stillbirth, and 11 abortions. Only 4 women denied a previous pregnancy or transfusion.

The 113 who had at least one surviving child had had a total of 189 successful pregnancies. These women also had had 3 transfusions and 27 unsuccessful pregnancies, including 4 neonatal deaths, 2 stillbirths, and 21 abortions. These latter pregnancies and transfusions were followed by the delivery of normal living children prior to the birth of one with erythroblastosis, so it may be assumed they had no relation to the production of immunization. The proportion of successful to unsuccessful pregnancies is approximately what could be expected in any group of normal women.

Unsuccessful Pregnancies Prior to Known Immunization but Not Followed by Delivery of a Normal Child.—It is impossible to know for certain whether these pregnancies belong to the period prior to immunization and are the pregnancies responsible for immunization or whether they may have been unsuccessful because of the action of antibodies. For this reason they have been kept separate. Most of these pregnancies were not observed in this hospital and there are very few records of antibody determinations; the few that were done showed no evidence that immunization was present. In this group are included 20 women who had 10 neonatal deaths or stillbirths and 12 abortions. Twelve women had transfusions either associated with the termination of the last pregnancy or unassociated with a pregnancy.

Pregnancies After Immunization but Preceding the Birth of a Living Erythroblastotic Infant at the Chicago Lying-in Hospital.—Twenty-four women had 35 such pregnancies. Delivered in other hospitals were 11 infants who survived, 7 who died, 4 that were stillborn, and 3 that were aborted. Delivered at the Chicago Lying-in Hospital were 2 who appeared normal in spite of being Rh positive, 3 who died, and 5 who were stillborn. All patients who had more than one living erythroblastotic infant at the Chicago Lying-in Hospital are considered as being in the first of these pregnancies so there are no living children listed among those who were delivered previously in this hospital.

*The word fetus as used in this paper refers to a product of conception dead at the time of delivery that weighs over 400 grams. Twenty-two weeks' gestation is the period beyond which the delivery of a dead fetus must be reported in Chicago. Since we believe weight is more accurate than the history of the last menstrual period, we have used 400 grams as the dividing line between reportable and nonreportable fetuses; where a fetus weighing less than 400 grams is meant, it is so designated or is called an abortion.

First Pregnancy at the Chicago Lying-in Hospital Resulting in the Birth of a Living Erythroblastotic infant.—One hundred thirty-three women gave birth to 136 surviving infants. This includes 6 sets of twins. In 3 sets both twins were Rh positive and both survived. In one set, one infant survived and one died, and in 2 sets one survived and one was stillborn.

Pregnancies Following the First Delivery of a Surviving Erythroblastotic Infant to a Patient in the Chicago Lying-in Hospital.—Twenty-nine women had 41 subsequent pregnancies. These terminated in the delivery of 14 surviving erythroblastotic infants, 10 who were stillborn, 5 who died neonatally, 5 that were aborted, and 7 who were unaffected. Of the latter, 3 were known to be Rh negative, one Rh positive and unaffected, and 3 of unknown Rh were delivered in other hospitals. Of the total of 41 pregnancies, there were 21, or 50 per cent, in which the infant survived. Of the 30 pregnancies which went beyond the period of abortion in which the fetus was known to be Rh positive there were 15 survivors, also 50 per cent.

Total Pregnancies.—

Before immunization: One hundred thirty-three women had 259 pregnancies prior to known immunization, or 1.9 per patient. Of these, 189, or 73 per cent, were successful, making 1.4 successful and 0.5 unsuccessful per patient. The 70 unsuccessful pregnancies (17 deaths, 9 stillbirths, and 44 abortions) were in 49 patients; 16 additional women had transfusions that contributed to immunization. In the entire group 65 women had unsuccessful pregnancies or transfusions, 64 had only normal pregnancies, and 4 had no history of transfusion or pregnancy. It was believed that in 21, or 15 per cent, of these women transfusion played an important role in the production of immunization.

After immunization: The 133 women had 212 pregnancies after immunization was known to have been established, or 1.80 per patient. Of these, 170, or 85.0 per cent, resulted in the birth of surviving infants. This figure includes 9 unaffected children; 3 known to be Rh positive, 3 Rh negative, and 3 of unknown Rh. The 42 unsuccessful pregnancies included 34 stillbirths or neonatal deaths and 8 abortions. Twenty-two occurred before the birth in this hospital of the living infant. The number of living infants per patient is 1.3, of unsuccessful pregnancies, 0.5.

All pregnancies per patient: These 133 women have had a total of 471 pregnancies, or 3.7 per patient. This includes 2.7 per patient that yielded a surviving infant and 1.0 per patient that were unsuccessful.

Pregnancy immediately preceding birth of a surviving erythroblastotic infant: Among 123 women whose first affected erythroblastotic infant survived, regardless of where it was born, the last preceding pregnancy terminated normally in 92 instances with a normal living infant and with no need for a maternal transfusion then or in the intervening period. The remaining 31 cases included 5 deaths, one stillbirth, 8 abortions, 15 transfusions (following a stillbirth in one, abortion in one, a normal child 2, and without pregnancy, 11) and 2 with no pregnancy. This is a frequency of 74.5 per cent who had neither a transfusion nor an unsuccessful pregnancy immediately preceding the birth of the erythroblastotic infant.

Considering all the pregnancies of our entire group of women, there were 155 in which an erythroblastotic infant survived. In these, 21, or 13.5 per cent, were immediately preceded by a death or stillbirth and 14, or 9 per cent, by an abortion. This leaves 77.5 per cent with a surviving child in the preceding pregnancy.

Pregnancies following the birth of a surviving erythroblastotic infant: If we investigate the entire group of mothers for the outcome of the next

pregnancy after a surviving erythroblastotic infant, regardless of whether these children were born at the Chicago Lying-in Hospital or elsewhere, we find the following: When the surviving child was the first erythroblastotic child to be delivered, 38 women had subsequent pregnancies terminating in 9 deaths, 9 stillbirths, 4 spontaneous abortions, 12 living affected infants, 2 Rh negative, and 2 normal infants of unknown Rh. There were only 8 additional cases in which there had been a pregnancy following the birth of a surviving erythroblastotic child who had not been the first child of that mother to be affected. The next pregnancy of these 8 terminated in one death, 2 stillbirths, 2 living erythroblastotic infants, one Rh-negative infant, and 2 of unknown Rh. If all pregnancies are considered, there is a 45.6 per cent survival of infants born after a surviving erythroblastotic infant has been previously delivered. If only the pregnancies progressing beyond the stage of abortion are included, there is a 50 per cent survival. This includes the Rh-negative and unaffected infants.

Mothers With Infants Who Died After Birth

Among the total pregnancies in our immunized women, 76 have terminated in the delivery of a living infant who succumbed after birth. In at least 3 instances erythroblastosis was believed in no way responsible for the death, but since the infants did have erythroblastosis, they are included here. Six of the mothers considered here are also included in the group with surviving infants, 5 of the infants who died having been preceded by a living infant delivered in this hospital and one being survived by a twin. There are only 65 mothers in the group with infants who died since 9 women had a second child who died and one had 2 subsequent children who did not survive.

Pregnancies Preceding Evidence of Immunization.—There were only 7 women who had no living children at the time a nonsurviving erythroblastotic child was born. Two had had no previous pregnancies and had been immunized by transfusions and 5 had had 10 unsuccessful pregnancies, including 5 infants who died in the neonatal period and 5 abortions. There was none without an earlier pregnancy or transfusion.

The other 58 patients had had 83 normal living children. Preceding the birth of the last living child, 5 of these women had had one death, 2 stillbirths, and 5 abortions. Two had been transfused in association with 2 of the abortions and 2 had been transfused following the birth of a normal infant, but in all cases a normal birth had followed subsequently.

Unsuccessful Pregnancies Prior to Known Immunization but Not Followed by Delivery of a Normal Child.—In the interval between the last normal pregnancy and the birth of the first infant recognized as being erythroblastotic, 13 women had 2 stillbirths, 14 abortions, and 5 transfusions.

Pregnancies After Immunization but Preceding the Birth of the First Erythroblastotic Infant to Die at the Chicago Lying-in Hospital.—Twenty-six women had 46 such pregnancies, 19 having been delivered elsewhere, and 7 having been delivered at our hospital. The outcome of these 46 pregnancies was 17 deaths, 17 stillbirths, 2 abortions, 10 living affected Rh-positive infants, and 2 living unaffected Rh-negative infants. Twelve, or 26.0 per cent, were successful.

Neonatal Deaths Among Erythroblastotic Infants.—There were 76 infants who died after birth: the length of survival was: less than 3 hours 25 (all except one lived less than 1½ hours), 3 to 24 hours 10, 25 to 48 hours 12, 49 to 72 hours 17, 73 to 96 hours 7, 4 to 13 days 5. Almost half the infants who failed to survive died during the first day of life. Among the 191 erythroblastotic infants born in this hospital in the past 20 years who survived the first 24 hours the mortality has been only 21 per cent. For the 261 who

lived at least 3 hours and who received some kind of treatment, the mortality was 24.4 per cent. Almost all of the infants who lived less than 3 hours were severely edematous. In many studies these hydropic infants who die almost immediately after birth have been considered in conjunction with the stillbirths and have not been included in the number of neonatal deaths.

Pregnancies Following the First Delivery of a Nonsurviving Erythroblastotic Infant to a Patient in the Chicago Lying-in Hospital.—Twenty-one of the 65 patients were delivered subsequently at the Chicago Lying-in Hospital and 5 were delivered elsewhere. (The latter figure includes 2 who were delivered of one child elsewhere and one at the Chicago Lying-in Hospital.) They had 36 pregnancies terminating in the birth of 3 surviving erythroblastotic and 2 Rh-negative infants, 12 infants who died, 8 who were stillborn, and the abortion of 11 fetuses. This is a survival of 14 per cent of all pregnancies, or 20 per cent of those that went beyond the stage of abortion.

Total Pregnancies.—

Before immunization: Sixty-five patients had 117 pregnancies prior to known immunization, or 1.8 pregnancies per patient. Of these, 83, or 71 per cent, were successful, making 1.3 successful and 0.5 unsuccessful per patient. If the abortions are eliminated, the survival becomes 83 of 93 pregnancies, or 90 per cent. The 34 unsuccessful pregnancies (6 deaths, 4 stillbirths, and 24 abortions) were in 18 women; 11 women (including 2 with abortions) had transfusions that contributed to immunization. In the entire group, 27, or 41.5 per cent, of the women had unsuccessful pregnancies or transfusions, 38, or 58.5 per cent, had only normal pregnancies.

After immunization: The 65 women had 149 such pregnancies, or 2.3 per patient. Of these, only 17, or 11.4 per cent, were successful. This includes 4 Rh-negative infants, leaving only 13 erythroblastotic infants who survived. The 132 unsuccessful pregnancies include 94 deaths, 25 stillbirths, and 13 abortions. The number of living children after immunization per patient is 0.3, of unsuccessful pregnancies is 2.0.

All pregnancies per patient: These 65 women have had a total of 266 pregnancies, or 4.1 per patient. This includes 1.6 living children per patient and 2.5 unsuccessful pregnancies.

Pregnancy immediately preceding the birth of an infant who died of Erythroblastosis After Birth: Among our total of 241 patients, there were 67 whose first erythroblastotic infant died after birth, either at our hospital or elsewhere. The pregnancy in which that child was delivered was immediately preceded by a normal infant in 45 instances, a death in 3, abortion in 11, abortion and transfusion in 2, only a transfusion in 5, and no known pregnancy or transfusion in 1. This is a frequency of 67.1 per cent who had only a normal pregnancy preceding the delivery of an erythroblastotic infant who died. Among 54 additional deaths that were preceded by the birth of an erythroblastotic infant, 9 of the preceding infants had lived, 12 had been stillborn, 29 had died, and 4 were aborted. In 16.6 per cent of this group the infant of the preceding pregnancy survived. Of the total of 121 infants who died neonatally of erythroblastosis, delivered by the women in the total series, 37.1 per cent followed the birth of a normal, nonerythroblastotic infant, 7.4 per cent followed the birth of a surviving erythroblastotic infant, and 55.5 per cent followed a pregnancy with an unsuccessful outcome.

Pregnancies following the birth of an infant who died neonatally of erythroblastosis: If the pregnancies following next in order after the one ending in the death of an erythroblastotic infant are examined, we find the following. When the first child with evidence of erythroblastosis died, the next

child to be delivered survived in 9 instances (6 erythroblastotic, 3 Rh-negative), died in 14, was stillborn in 12, and was aborted in 8. This is a total survival of 9 in 43 pregnancies, or 20.9 per cent. If abortions are omitted from the calculations, it is a survival of 25.7 per cent. In 24 instances where the child who died was not the first affected offspring, the outcome in the next following pregnancy was the same as when the child who died was the first affected infant. There were 5 living infants (3 affected, 1 Rh-negative, 1 Rh-positive but normal) in a total of 24 such pregnancies, giving a survival of 20.8 or, if abortions are excluded, of 25 per cent.

Mothers With Stillborn Fetuses

Seventy-seven stillborn fetuses with erythroblastosis have been delivered by 62 women. In 2 instances both of the twins were stillborn, 9 women were delivered of a second stillborn erythroblastotic infant, and 2 women were delivered of 2 subsequently stillborn erythroblastotic fetuses.

Pregnancies Preceding Evidence of Immunization.—There were 11 women who had no living children at the time of the delivery of the first stillborn erythroblastotic fetus. Four had had no pregnancies and had been immunized by transfusions. Seven others had had 5 stillbirths (presumably not erythroblastotic), 2 neonatal deaths, and 8 abortions, 3 of which were followed by transfusions. Seven of the 11 were believed to have been immunized by transfusions. The remaining 51 women had 81 living nonerythroblastotic infants and, preceding the birth of the last normal child, 8 women had had 2 stillbirths, one neonatal death, and 5 abortions, one of which was followed by 2 transfusions.

Unsuccessful Pregnancies Preceding Known Immunization but Not Followed by a Normal Infant.—During this time 18 women had 26 unsuccessful pregnancies; these included 5 stillbirths, 4 neonatal deaths, 17 abortions, 4 of which were followed by transfusions. There were 3 additional women who had had a transfusion after the birth of a normal child or unassociated with pregnancy.

Pregnancies After Immunization but Preceding the Birth of a Stillborn Fetus at the Chicago Lying-in Hospital.—Thirty-two women had had 66 erythroblastotic infants previously. Delivered at other hospitals were 19 women whose pregnancies ended in 2 surviving infants, 12 neonatal deaths, 14 stillbirths, and 16 abortions; at the Chicago Lying-in Hospital there were 15 women with 12 living erythroblastotic infants, 2 Rh-negative infants, 2 infants who died neonatally, and 6 abortions. Two women are included in both groups.

Pregnancies Following the First Stillborn Erythroblastoic Fetus to Be Delivered at the Chicago Lying-in Hospital.—Nineteen women have had 28 subsequent pregnancies (plus 2 terminating in therapeutic abortions not included). These terminated in the delivery of 2 normal Rh-negative infants, 2 Rh-positive severely erythroblastotic infants who survived, 5 who died, 15 who were stillborn, 4 spontaneously aborted. This is a survival of 4 in a total of 28 pregnancies (14.3 per cent) or 2 in 22 Rh-positive fetuses that went beyond the stage of abortion (9.0 per cent).

Total Pregnancies.—

Before immunization: The total number of pregnancies in this group of 62 women is 130, or 2.1 pregnancies per patient. Of these, 81, or 62.3 per cent, were successful, giving an average of 1.3 living children per patient, and 0.8 unsuccessful pregnancies. The 49 unsuccessful pregnancies (7 deaths, 12 stillbirths, 30 abortions) occurred among 33 women; 7 additional women had transfusions but no unsuccessful pregnancies. In the entire group, 40 women

had an unsuccessful pregnancy or a transfusion preceding evidence of immunization; only 22, or 35.5 per cent, had had only normal pregnancies. It was believed that in 15, or 24.2 per cent, transfusion was an important factor contributing to immunization.

After immunization: The 62 women who had stillborn erythroblastotic infants in this hospital had a total of 156 pregnancies during which evidence of immunization was present. This is an average of 2.5 per patient. Of these 20 terminated in living infants (16 surviving affected infants and 4 Rh-negative infants). The remaining 136 terminated in 19 deaths, 91 stillbirths, and 26 abortions. Only 12 per cent of the pregnancies were successful in producing a living infant. The frequency per patient of unsuccessful pregnancies is 2.2, of living infants 0.4.

All pregnancies per patient: These 62 women have had a total of 286 pregnancies, or 4.7 per patient. This includes 1.7 successful and 3.0 unsuccessful.

Pregnancy immediately preceding the birth of a surviving erythroblastotic Infant: Among 51 women in our entire group of 241 whose first pregnancy after immunization terminated in an erythroblastotic stillborn fetus, the preceding pregnancy terminated in 34 normal infants, one death, and 13 abortions. Three had had only transfusions, and in 4 more a transfusion had accompanied an abortion. There were 72 additional erythroblastotic stillborn infants not from the first pregnancy after immunization was present. The pregnancy immediately preceding these stillbirths terminated in 11 living erythroblastotic infants, one normal Rh-positive and 2 normal Rh-negative infants, 14 deaths and 33 stillbirths from erythroblastosis and 11 abortions. Of the total of 123 stillbirths, only 37, or 30 per cent, followed the birth of a normal nonerythroblastotic infant.

Pregnancies following the birth of a stillborn erythroblastotic fetus: If we look at the pregnancies that have followed the birth of the first erythroblastotic infant when that child was stillborn (regardless of whether or not that particular child was born at the Chicago Lying-in Hospital), we find 34 women with subsequent pregnancies. Those immediately following the first stillborn erythroblastotic fetus terminated in the birth of 3 surviving erythroblastotic infants, one normal Rh-negative infant, 7 who died, 16 who were stillborn from erythroblastosis, and 7 abortions. This is a survival of 11.7 per cent (4 in 34) in all pregnancies, or 11.4 per cent (3 in 26) of the Rh-positive fetuses who passed the stage of abortion. In a total of 82 subsequent pregnancies in these women, the result was 8 surviving affected infants and 3 Rh-negative infants, 17 deaths, 40 stillbirths, and 14 abortions. This is a total survival of 13.4 per cent, or 12.3 per cent of 65 pregnancies which went beyond the stage of abortion and in which the fetus was Rh positive.

If in all women the pregnancy that followed immediately after the delivery of a stillborn erythroblastotic infant is considered, regardless of the position of the stillbirth in relation to other erythroblastotic infants, we have a total of 103. The next pregnancy terminated in a stillbirth in 48 instances, a death in 29, a spontaneous abortion in 17, a living erythroblastotic child in 6, an unaffected Rh-positive child in one, and an Rh-negative child in 2. This is a frequency of survival of 9 in 103, or 9.1 per cent; or of 8 in 85 Rh-positive fetuses who passed the stage of abortion, making 9.4 per cent.

There is very little difference in the outcome of a pregnancy that follows the delivery of a stillborn fetus in which that fetus is the first affected erythroblastotic infant to be delivered and one in which the erythroblastotic stillborn infant has been preceded by other erythroblastotic infants. In either case the total survival rate is approximately 10 per cent.

Comment

The case histories analyzed in this report extend back 20 years, all of our cases having been used in order to follow our patients as many years as possible. It means, consequently, that we have a total of fewer living children than if it had been possible to use only current pregnancies, since the diagnosis was rarely made in a living child until 10 years ago, and it means also that some of the deaths and stillbirths that were regarded as occurring in the first erythroblastotic child were doubtless preceded by some affected but living infants whose cases were not diagnosed. The subsequent pregnancies, however—those in which we are especially interested—show practically no difference today from those observed many years ago. Among currently observed infants there are fewer deaths and more survivors than in the entire group, but the proportion of stillbirths among affected infants remains the same. Of the total of 302 erythroblastotic infants observed in this hospital, 49.3 per cent survived, 25.2 per cent died, and 25.5 per cent were stillborn. For the past 10 years the survival rate has increased to 58 per cent (132 of 230 cases), the deaths have decreased to 19 per cent (44 of 230 cases), and the stillbirths to 23 per cent (54 in 230 cases). In the last 4 years the survival has been 64 per cent (72 of 113 cases), deaths 14 per cent (16 of 113 cases), and stillbirths 22 per cent (25 in 113 cases).

Of all 241 women observed during 20 years, half have given birth to living children in their first pregnancy with erythroblastosis. There were 171 who had had only normal living children and had had no transfusions before the birth of their first erythroblastotic child. The first affected infant survived in 92 (53.8 per cent) of these cases, died in 45 (26.2 per cent, and was stillborn in 34 (20 per cent). Of the 123 women whose first affected child lived, 74.5 per cent had had neither an unsuccessful pregnancy nor a transfusion; of the 67 whose first affected child died, 67.1 per cent had had neither an unsuccessful pregnancy nor a transfusion; and of the 51 whose first affected child was stillborn, 66.7 per cent had had only normal children.

These figures are at variance with the often repeated statement that the disease can always be expected to be more severe in succeeding pregnancies. Although more first affected children live than die or are stillborn, the siblings of these surviving children will also have a greater chance of surviving. In this series the child following the birth of any surviving erythroblastotic infant also survived in 50 per cent of the cases. Following a stillbirth from erythroblastosis, the next child survived only 10 per cent of the time. From this and from inspection of individual case histories, it seems as if in some instances maternal immunization affected all offspring only mildly while in others the majority were severely affected.

Everyone is familiar with the woman who has had repeated stillbirths and, on the other hand, with women who, although they have antibodies, have had several infants in whom the disease was so mild that there was some question as to whether the diagnosis should actually be made.

Our mothers whose first affected child survived have had fewer succeeding pregnancies than those who have had stillbirths and few of those who have had a second living child have had subsequent pregnancies. There were only 14 who did have more than one pregnancy subsequently and all but 2 of these had a later death or stillbirth. Two women have had 3 pregnancies, in each of which erythroblastotic infants survived, and a third had 2 surviving erythroblastotic and one Rh-negative infants.

Summary

The outlook for a successful pregnancy in a woman immunized to Rh is never hopeless, and the outcome of a subsequent pregnancy can never be predicted with certainty.

An analysis of the histories of 241 women delivered of 302 infants at the Chicago Lying-in Hospital after they became immunized shows that the outcome of any given pregnancy is related to the outcome of the pregnancy immediately preceding it. Following the birth of a surviving erythroblastotic infant, the next child survived approximately 50 per cent of the time. After the birth of a child who died, the next child survived 20 per cent of the time. After a stillbirth, the survival was only 10 per cent. With the improvement in treatment that is currently taking place, a somewhat larger percentage of infants should survive in the future.

Women who have had stillborn erythroblastotic infants have had more total pregnancies following immunization than those whose erythroblastotic infants were born alive; before immunization they had about the same number. Those who had a surviving erythroblastotic infant born at the Chicago Lying-in Hospital had an average of 1.9 pregnancies before immunization and 1.8 subsequently. Those with an infant who died had an average before immunization of 1.8 pregnancies and after immunization of 2.3. Those with a stillborn fetus had 2.1 pregnancies before immunization and 2.6 subsequently. The first group averaged 2.7 total surviving infants, 1.0 not surviving; the second group averaged 1.6 surviving, 2.5 not surviving; the third group averaged 1.7 surviving, 3.0 not surviving.

The variability in the outcome of pregnancy in which immunization is present must be taken into account in the attempt to evaluate any method of prevention or treatment of erythroblastosis.

THE DIAGNOSIS AND TREATMENT OF ERYTHROBLASTOSIS FETALIS*

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THE diagnosis of erythroblastosis due to the Rh factor depends on (1) proof of isoimmunization of the mother to the Rh-positive blood of the fetus by the detection of anti-Rh maternal antibodies, (2) demonstration of the transference of the maternal antibodies to the fetus, and (3) the recognition of clinical and hematological signs of excessive blood destruction and regeneration in the newborn infant.

Classification

A classification of the degree to which the infant is affected at birth, which we have employed at the Chicago Lying-in Hospital for the past 5 years, is given in Table I.

Infants classified as nonaffected are not included in this discussion.

Infants classified as mildly ill at birth are vigorous, show minimal signs of pallor, splenomegaly, or hepatomegaly, and only a mild degree of anemia; the hemoglobin levels in the cord blood are above 13.5 and above 14 Gm. in the heel blood. More recently, we have found that the level of 15 Gm. in the heel blood would probably be a more reasonable value than 14 Gm., since it correlates better with the high bilirubin levels in the cord blood and the need for early treatment. The reticulocyte count is elevated and erythroblastemia is mild. These mildly affected infants develop clinical jaundice within the first few hours of extrauterine life, but seldom show a rapid fall in the hemoglobin levels. The serum bilirubin levels rise significantly and to a variable degree within the first 18 hours of life and may reach a critical level between 24 and 72 hours after birth. Serial determinations of the bilirubin levels in the serum obtained by heel blood puncture at the interval of 8, 12, or 18 hours dependent upon the pre-existing levels provide a reliable indication of the progression of the hemolytic process. Of 217 infants treated, 109, or 50 per cent, were classified as mildly ill at birth.

Infants moderately ill at birth usually exhibit notable sings of pallor, more pronounced enlargement of the liver and spleen, and are often less active than the normal infant. The hemoglobin is less than 13.5 Gm. per cent in the cord blood and less than 14 Gm. per cent in the heel blood. A fall in the hemoglobin level occurs frequently though not regularly in the first 24 hours of life. The

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percentage of circulating erythroblasts is high at birth and remains high during the first day or two of life. The bilirubin levels in the cord blood are higher, as a rule, than in the mildly affected infants, although there is no direct correlation between the hemoglobin and the bilirubin levels in the cord blood regularly. Of 217 infants treated between 1945 and 1956, 42 or 19.3 per cent, were classified as moderately ill at birth. Since the adoption of the exchange transfusion regime, all such infants receive an exchange within the first few hours of life.

Infants severely affected at birth should be subclassified as (1) severely and (2) extremely ill according to their general circulatory and respiratory status. The severely ill group exhibit marked pallor, hepato- and splenomegaly, and hematological signs of severe anemia with hemoglobin levels below 11 Gm. per cent in the cord blood, marked erythroblastemia, and often a thrombocytopenia. Although listless and weak, the infant's circulatory and respiratory function is adequate to sustain life. This group is potentially salvageable with immediate exchange transfusion therapy. The extremely ill group of infants show even more severe signs of pallor, complicated by cyanosis, hemorrhagic manifestations, such as petechiae or purpura, hemoglobin levels below 9 Gm. per cent, and some degree of edema. Respirations are maintained only with artificial measures. These extremely affected infants rarely survive, in spite of an attempt to give an immediate exchange transfusion. Of the 217 cases treated within the past 12 years, 51 cases, or 23.3 per cent, were in these severely ill groups, and 6 of the 51 died without establishing independent respirations within 90 minutes after birth.

The hydropic infants are moribund on delivery; severe anemia, pallor, generalized edema, respiratory and circulatory failure are incompatible with life. In our experience, of the 15 hydropic infants among the total of 217 affected babies delivered in the past 12 years, none survived although an exchange was accomplished in 3 cases.

TABLE I. CLASSIFICATION OF SEVERITY OF DISEASE AT BIRTH

I. No Disease.—		
		1. A positive Coombs test in the infant and/or
		2. A rising titer of maternal antibodies during pregnancy
II. Mildly Affected.—		
At Birth:		1. The above serological signs of isosensitization
		2. Cord hemoglobin above 13 Gm. or heel blood of 14 Gm. or more
		3. Pallor, splenomegaly, and normoblastosis
Later:		4. Jaundice which appears within the first 24 hours of life, and deepens
		5. Mild, the anemia or icterus progressive, but behavior of the infant remains good
III. Moderately Severe Disease.—		
At Birth:		1. Hemoglobin less than 13.5 Gm. but more than 11 Gm.
		2. Spleno- and hepatomegaly
		3. Excessive normoblastosis
Later:		4. Early signs of deepening jaundice, anemia, purpura, or edema
IV. Severely Affected.—		
At Birth:		
	A.	1. Hemoglobin less than 11 Gm.
		2. Marked hepato- and splenomegaly
		3. Pallor and listlessness
		4. Excessive normoblastosis and thrombocytopenia
		5. Circulatory and respiratory function adequate to sustain life
	B.	1. Hemoglobin less than 9 Gm.
		2. Above signs of severe erythroblastosis, plus edema and/or purpura
		3. Circulatory and/or respiratory function inadequate to sustain life

The major causes of death in liveborn infants affected with Rh erythroblastosis are: (1) hydrops fetalis, (2) extreme erythroblastosis with anemia, erythroblastosis of the extramedullary organs of hematopoiesis, disturbance of the clotting mechanisms due to thrombocytopenia and/or hepatic dysfunction, and (3) kernicterus. The causes of death in 47 of 217 cases of Rh erythroblastosis delivered at the hospital between 1945 and 1956 are given in Table II. Hydrops fetalis accounted for 15, or 32 per cent, of the death; deaths occurred within 14 to 105 minutes after birth. Extreme erythroblastosis accounted for 6 deaths; all of these 6 infants required artificial respiration and cardiac stimulation to maintain life even so short a time. Four of the 6 infants received one exchange. These 6 infants were probably not salvageable. Kernicterus was the cause of death in 14, or 29.8 per cent, of the 47 babies who died; 5 of the 14 babies who died of kernicterus received a single exchange transfusion. No infant who received more than one exchange has died of kernicterus in our series of 217 cases. In 7 cases, pulmonary hemorrhage and purpura were associated with the findings of extreme erythroblastosis. In one case a hemorrhage into the abdominal wall occurred following an unsuccessful attempt at an exchange transfusion in a severely ill infant; this accident occurred in 1950 in the early period of our experience with the technique, and has not happened again. Three infants died with hyaline membrane disease; 2 were born spontaneously and one by cesarean section, none was born prematurely; all were severely affected at birth. Cardiac failure developed on the second day of life in a large baby delivered of a diabetic mother; the infant was mildly affected at birth, and an exchange was performed on the second day of life, when hyperbilirubinemia developed; the cardiac status deteriorated rapidly after the exchange, and the course of events leads us to feel that in the particular infant who could be expected to develop a cardiac complication as a result of the maternal diabetes, the exchange was poorly timed; an earlier exchange might have prevented the death. A subsequent pregnancy in this same diabetic mother terminated in a cesarean delivery of another affected infant in 1957. The baby was mildly affected at birth; an exchange transfusion was performed within the first 6 hours of life, and the course throughout the newborn period was uneventful.

TABLE II. CAUSES OF DEATH IN 47 OF 217 LIVEBORN AFFECTED BABIES WITH RH ERYTHROBLASTOSIS

MAJOR CAUSE OF DEATH	DEATHS		TREATMENT			DURATION OF LIFE	
	NUMBER	%	NONE	STANDARD TRANSFUSIONS	EXCHANGE	AVERAGE	RANGE
Hydrops fetalis	15	32.0	8	4	3	49 minutes	14-105 minutes
Extreme erythroblastosis at birth	6	12.7	1	1	4	60 minutes	10- 90 minutes
Kernicterus	14	29.8	1	8	5	65 hours	32-120 minutes
Pulmonary hemorrhage	4	8.5		1	3	35½ hours	7- 77 hours
Pulmonary hyaline membrane	3	6.3		0	3	28 hours	18- 36 hours
Erythroblastosis and purpura	3	6.3		3		18½ hours	12½-18 hours
Hemorrhage	1	2.4		1		84 hours	
Cardiac failure	1	2.4		0	1	39 hours	
Total deaths	47		10	18	19		

A critical review of these deaths in the light of our experience with our present regime would permit one to expect that the preventable deaths were

those exclusive of the 21 cases of fetal hydrops and extremely severe erythroblastosis, or that 26 infants were possibly salvageable.

Therapy

The dual objectives of therapy for erythroblastosis are (1) the removal of the products of blood destruction before irreversible damage occurs to vital tissue, and (2) correction of anemia. In infants mildly affected at birth, who do not require blood for the correction of anemia, the most reliable criterion of the progression of the hemolytic process is the chemical evaluation of the level of hyperbilirubinemia. The sole origin of bilirubin is hemoglobin; in the normal newborn infant the relative inefficiency of the liver to excrete bilirubin in the first 3 days of life is largely responsible for the development of icterus neonatorum, and the rapid clearance of jaundice in the latter part of the first week of life correlates with improvement in hepatic function. The normal levels of serum bilirubin at birth and throughout the newborn period are well established and recently Hsia, Allen, and their associates[1] reported the bilirubin levels obtained in normal infants whose blood type was compatible with the mother's blood and also the levels obtained in normal infants whose blood type in the ABO system was not compatible. In the normal "compatible" infants the cord serum bilirubin levels ranged from 1.4 to 3.2 mg. per cent; the maximum elevation of the bilirubin levels occurred on the third day of neonatal life with a range of 3.1 to 12 mg. per cent. In the normal "incompatible" infants the serum bilirubin levels were similar to those of the "compatible" infants.

The critical level beyond which clinical or pathological signs of kernicterus develop varies with the age of the infant and the rapidity of the accumulation of the products of blood destruction, coincident with the hemolytic process. Hsia and collaborators[1] found that the incidence of kernicterus correlated with serum bilirubin levels of 30 mg. per cent, and demonstrated that symptoms of encephalopathy were avoided by maintaining levels below 20 mg. per cent throughout the newborn period. Mollison[2] analyzed a large series of cases of Rh erythroblastosis collected from several centers in England, and found that the hemoglobin level in the cord blood was a rough indicator of the severity of disease. The experience of numerous investigators reported in the past 5 years establishes the validity of the prognostic value of the hemoglobin level at birth, and the reliability of the serum bilirubin levels throughout the first 5 days of life as indicators for the use of exchange transfusion therapy. Additional information is obtained by measurements of the plasma heme pigments in the cord blood; Boggs and Abelson[3] demonstrated that abnormal amounts of hematin and methalbumin in the cord blood correlated better with the severity of disease than did the bilirubin levels.

In cases of erythroblastosis treated by us in the past 2 years data were collected which permit a comparison of the hemoglobin and bilirubin levels in the cord blood. In Table III the hemoglobin and the bilirubin levels in the cord blood are correlated with the timing of the exchange transfusion. In 9 of 14 infants whose hemoglobin values at birth were in the anemic range of 4 to 15 Gm., the cord serum bilirubin levels were elevated above 5 mg. per cent. However, the correlation was poor in 5 of these anemic infants; in one hydropic infant, the hemoglobin was 4 Gm. and the bilirubin in the cord serum was only 1.2 mg. per cent. Twelve of these 14 infants who were anemic at birth were treated with an exchange transfusion within the first 6 hours of life. The early exchange did not protect against a further rise in the bilirubin levels during the next few hours; 5 infants required more than one exchange within the first 4 days of life.

TABLE III. CORRELATION OF HEMOGLOBIN LEVEL BELOW 15 GM. AT BIRTH AND REQUIREMENT FOR EXCHANGE

CASE NUMBER	HEMOGLOBIN AT BIRTH (GM.)	BILIRUBIN CORD (MG.)	BILIRUBIN LEVELS (MG. %) DETERMINATION AT TIME OF TRANSFUSION (*) BY AGE IN HOURS									EXCHANGE TRANSFUSIONS
			0-6	7-12	13-18	19-24	25-36	37-48	49-60	61-72	73-84	
42	4.0	1.2	*									Incomplete. Died ½ hour
24	60.0	6.8	*									1 Died ½ hour
2	9.6	7.5	*									1 Lived
26	11.0	5.7	*									1 Lived
8	11.0	3.5	*									1 Lived
40	11.0	2.1	*									1 Lived
43	11.4	6.9								20.0*		1 Lived
1	11.5	8.5	*			14.0*		21.5*				3 Lived
7	11.6	3.7	*					13.5*				2 Lived
23	12.3	12.0	*		22.0*		21.0*		28.0*		45.0*	5 Lived
3	12.8	6.6	*		13.0*							2 Lived
5	13.7	6.0	*						19.8*			2 Lived
25	14.5	6.1					20.0*					1 Lived
9	15.0	3.0	*									1 Lived

Total 14 cases

In 11 of 12 infants whose hemoglobin at birth was above 15 mg. (Table IV), the bilirubin levels in the cord blood were below 5 mg. per cent. Exchange transfusion was performed in 3 of 12 cases within the first 6 hours of life, and each required a second exchange. Four infants received their first exchange between 12 and 18 hours after birth, and 6 at 36 to 48 hours of life. Six of these infants who were mildly ill at birth required two or more exchanges. The critical level of around 20 mg. per cent bilirubin was reached at 37 to 48 hours in the majority of the cases. All of these infants survived without signs of encephalopathy.

TABLE IV. CORRELATION OF HEMOGLOBIN LEVELS ABOVE 15 GM. AT BIRTH WITH REQUIREMENT FOR EXCHANGE

CASE NUMBER	HEMOGLOBIN AT BIRTH (GM.)	BILIRUBIN CORD (MG.)	BILIRUBIN LEVELS (MG. %) DETERMINATION AT TIME OF TRANSFUSION (*) BY AGE IN HOURS									EXCHANGE TRANSFUSIONS
			0-6	7-12	13-18	19-24	25-36	37-48	49-60	61-72	73-84	
28	15.5	4.5					17.0*					1 Lived
37	16.0	2.6		9.8*				19.0*				3 Lived
4	16.0	6.4		16.3*				22.0*				2 Lived
11	16.2	2.7						16.0*				1 Lived
16	16.5		5*					19.0*				2 Lived
27	16.5	4.5			15.0*							1 Lived
41	17.0	1.9	*									1 Lived
31	17.5	3.7			15.3*			24.6*				2 Lived
34	17.9	2.8						18.0*		8.7*		2 Lived
6	19.0	3.8	12*					26.0*				2 Lived
38	17.7	2.6						22.0*				1 Lived
12	20.0	2.6						20.1*				1 Lived

Total 12 cases

Direct evidence of the toxicity of bilirubin was presented by Day,[4] who demonstrated that crystalline bilirubin reduces the oxygen uptake of homogenates of rat brains in vitro. This inhibition was reversed by cytochrome C. The toxic effect of bilirubin on adult rat brain is reversible, but it appears to be

lethal to the brain of the newborn rat. Further, he found that hematin was toxic for brain and diaphragm tissue homogenate. These recent investigations indicate that there is reason to be guarded in concluding that either bilirubin or any other one product of erythrocyte metabolism is the essential cause of encephalopathy in hemolytic disease. The presence of these substances in excessive amounts may have an additive noxious effect. At the present time other factors such as an immaturity of the enzyme system of newborn brain, or even of newborn liver, or variations in the permeability of the blood-brain barrier, or anoxia secondary to pulmonary complications common in the severe form of the disease are unknown facets of this problem.

In our program for the management of hemolytic disease of the newborn at the Chicago Lying-in Hospital, the serum bilirubin levels have been employed as an adjunct to the clinical decision for exchange transfusion for the past several years. This test has proved most useful in timing the need for the first exchange transfusion in infants who appeared mildly ill at birth, but who exhibited no signs of a rapidly progressing hemolytic process, and also as an indication for repeating the exchange in the more severely affected infants. An exchange transfusion has been performed at birth or shortly thereafter in all infants classified as moderately or severely ill at birth according to the criteria given above.

The success of the exchange regime depends upon the cooperative effort of a trained team of obstetricians, pediatricians, nurses, and laboratory assistants. The obstetrician must anticipate the birth of an affected infant, notify the pediatrician when the patient goes into labor, and conduct the delivery by the most conservative method possible and prepare the cord for the best manipulation of the catheter. The pediatric exchange transfusion team must be skilled in the technique of the method of transfusion, not only by the umbilical route, but also by an alternate route such as the saphenous vein if multiple transfusions are necessary. The pediatrician must be able to do the necessary diagnostic serological and hematological procedures and to perform the chemical determinations for bilirubin during the hours when the laboratory assistants are not available. The results of our program are largely due to the enthusiasm of the exchange team of house staff pediatricians and their meticulous observation of the infants throughout the first critical week of life.

Results

The results of the treatment of 217 cases of erythroblastosis treated in the past 12 years were analyzed in the following mortality statistics (Table V). The column to the left presents the mortality rate per year for all liveborn affected infants. The mortality rate has varied in different years from 50 to 5 per cent, the lowest rate occurring within the past 7 years. In the column to the right, 21 infants who died within 90 minutes of life are excluded. These were 15 with hydrops fetalis, and 6 with extremely severe erythroblastosis who never established independent respiration.

In these 196 viable infants the fall in the mortality rate in the past 5 years is demonstrated more clearly. This favorable change in the mortality rate in recent years is shown more graphically in Table VI which divides the total series of cases into two groups: 113 cases treated between 1945 and 1951, and 104 cases treated between 1952 and 1956. In the group treated prior to 1951, 33, or 29.2 per cent, of the infants died. Of the group of 104 cases treated in the 5 year period, 1952 to 1956, 14, or 13 per cent, died. The exclusion of 26 affected infants, probably unsalvageable, leaves a total of 196 affected babies

in the total series; of 101 infants delivered between 1945 and 1951, 21, or 20.8 per cent, died; of 95 delivered between 1952 and 1956, 5, or 5.3 per cent, died. The improvement in the mortality rate in the past 5 years is due largely to the change in the rationale of therapy, and the employment of exchange transfusions which keep the accumulation of the products of blood destruction within tolerable limits within the first 4 days of life. To demonstrate the favorable effect of this therapeutic regime it is necessary to analyze the mortality statistics both for the treatment employed and for the severity of disease in the cases treated.

TABLE V. MORTALITY RATE OF RH ERYTHROBLASTOSIS IN LIVEBORN AFFECTED INFANTS BORN AT THE CHICAGO LYING-IN HOSPITAL BETWEEN 1945 AND 1956

	ALL LIVEBORN AFFECTED INFANTS			AFFECTED INFANTS WHO SURVIVED LONGER THAN 90 MINUTES		
YEAR	CASES	DEATHS	UNCORRECTED MORTALITY RATE (%)	CASES	DEATHS	CORRECTED MORTALITY RATE (%)
1945	16	6	37.5	13	3	23.0
1946	16	5	31.2	14	3	21.0
1947	15	4	26.7	15	4	25.6
1948	11	5	45.4	9	3	33.0
1949	12	6	50.0	8	2	25.0
1950	18	2	11.1	17	1	5.9
1951	25	5	20.0	25	5	20.0
1952	25	3	12.0	24	2	8.3
1953	16	1	6.2	15	0	0.0
1954	22	6	27.4	19	3	15.7
1955	20	1	5.0	19	0	0.0
1956	21	3	14.3	18	0	0.0
Total	217	47		196	26	

TABLE VI. CHANGE IN THE MORTALITY RATE OF LIVEBORN BABIES WITH RH ERYTHROBLASTOSIS DELIVERED AT THE CHICAGO LYING-IN HOSPITAL DURING THE PAST 5 YEARS

	ALL LIVEBORN AFFECTED BABIES			AFFECTED BABIES WHO SURVIVED LONGER THAN 90 MINUTES		
DATES	CASES	DEATHS	UNCORRECTED MORTALITY RATE (%)	CASES	DEATHS	CORRECTED MORTALITY RATE (%)
1945 to 1951	113	33	29.2	101	21	20.8
1952 to 1956	104	14	13.4	95	5	5.3
Total	217	47		196	26	

In the total series of 217 cases (Table VII) in which there were 47, or 21.7 per cent, deaths, 109, or 50 per cent, of the infants were mildly affected at birth; 42, or 19.3 per cent, were moderately ill at birth, and 51, or 23 per cent, were severely affected at birth; 15, or 6.9 per cent, were hydropic infants. Of the 40 who received no transfusions, 12, or 30 per cent, died. Thirty-one, or 77.5 per cent, of these 40 infants were mildly ill at birth, and 9 babies were hydropic or extremely ill at birth; thus, the percentage of either mildly ill or hydropic infants is higher in this group than in those treated with transfusions. Of the 74 cases treated with standard small transfusions, 15, or 20 per cent, died; 55 per cent of these 74 infants were mildly ill at birth, 18.9 per cent were severely ill at birth, and 5.5 per cent were hydropic; the percentage of the combined groups of moderately and severely ill babies was 39 per cent, a lower

TABLE VII. DEATHS WHICH OCCURRED AMONG 217 LIVEBORN INFANTS WITH RH ERYTHROBLASTOSIS DELIVERED AT THE CHICAGO LYING-IN HOSPITAL FROM 1945 TO 1956 CORRELATED WITH THE SEVERITY OF THE DISEASE AT BIRTH AND WITH TREATMENT

TRANSFUSION	NUMBER OF CASES	DEATHS		SEVERITY OF DISEASE AT BIRTH							
				MILD		MODERATE		SEVERE		HYDROPS	
		NUMBER	%	NO.	%	NO.	%	NO.	%	NO.	%
No transfusion	40	12	30.0	31	77.5	0		1	2.5	8	20.0
Standard transfusion	74	15	20.0	41	55.5	15	20.1	14	18.9	4	5.5
Exchanged											
Once	71	19	27.2	28	39.4	17	23.9	23	32.4	3	4.2
Twice or more	32	1	3.3	9	28.1	10	31.2	13	40.7		
Total	217	47	21.7	109	50.2	42	19.3	51	23.3	15	6.9

TABLE VIII. DEATHS WHICH OCCURRED AMONG 196 LIVEBORN INFANTS WITH RH ERYTHROBLASTOSIS WHO SURVIVED LONGER THAN 90 MINUTES CORRELATED WITH THE SEVERITY OF DISEASE AND WITH THE TREATMENT

TRANSFUSIONS	NUMBER OF CASES	DEATHS		SEVERITY OF DISEASE AT BIRTH						
				MILD		MODERATE		SEVERE		
		NUMBER	%	NO.	%	NO.	%	NO.	%	HYDROPS
None	31	3	9.7	31	100					0
Standard transfusion	69	10	14.5	41	59.5	15	22	13	18.5	0
One exchange transfusion	64	12	18.7	28	43.6	17	26.6	19	29.8	0
Two exchange transfusions	32	1	3.1	9	28.1	10	31.2	13	40.7	0
Total	196	26		109	55.5	42	21.4	45	24	0

figure than the percentage of similarly affected infants treated with exchange transfusions. In the group of 103 infants treated with exchange transfusions, 20 babies died; of 71 treated with a single exchange, 19, or 27 per cent, died; and of 32 treated with multiple transfusions, 1, or 3 per cent, died. To evaluate the difference in the mortality rates, particularly in the cases treated with one or several transfusions, it is better to compare the data in Table VIII which eliminate the 3 extremely affected infants and 3 hydropic infants. Here it is seen that of 64 treated with one exchange, 12, or 18.7 per cent, died; 43 per cent of the infants were mildly ill at birth, 26 per cent were moderately ill, and 29 per cent were severely ill at birth. Of the 32 who received repeated exchange transfusions, one, or 3.1 per cent, died; 28 per cent of these were mildly ill, 31.2 per cent were moderately ill, and 40.7 per cent were severely ill at birth. The mortality rate of the total of 196 babies who were able to establish an independent life with variable degrees of illness due to Rh erythroblastosis, treated with exchange transfusion, was 13.4 per cent. The low figure of 3.1 per cent deaths achieved with multiple transfusions provides a goal, but assumes that the infant is able to survive long enough to receive a second exchange, a condition which depends to a large extent upon the degree of intrauterine hemolysis, and it is expected that a figure median to the results achieved by the single and multiple exchanges would be a truer one.

Treatment of Rh Erythroblastosis at the Bobs Roberts Memorial Hospital for Children

Until the past few years, the results of treatment of Rh erythroblastosis reported from children's hospitals have been less favorable than those reported from lying-in hospitals.[5] Delay in transferring the case to the pediatric hospital has resulted either in a high percentage of deaths or the late development of the sequelae of kernicterus. The results of cases treated at the Bobs Roberts Children's Hospital after referral from general hospitals in the Chicago area illustrate the unfavorable effect of delay in the referral upon the results of treatment.

Table IX analyzes the data on 47 cases of Rh erythroblastosis referred to the Bobs Roberts Hospital between 1945 and 1956, according to age of the baby on admission and the treatment employed. During the period 1945 to 1951, 25 infants were admitted; there were no deaths; 23 infants were treated with standard transfusions and 2 received exchange transfusions. Since 13, or 50 per cent, of the babies were admitted after the fifth day of life, those severely ill at birth were thereby eliminated. Forty per cent of the infants were admitted after the tenth day of life for treatment of the anemia. On the other hand, of 22 admitted between 1952 and 1956, 12, or 54 per cent, were admitted on the first day of life; 2 infants, a set of twins, were admitted on the 3rd day of life with severe clinical signs of kernicterus and died on the fourth day in spite of an exchange. A third infant who was moribund on arrival died on the first day of life before an exchange was completed. The mortality rate in the 47 referred cases treated in the past 5 years was 13.6 per cent, a figure similar to the uncorrected figure obtained at the Chicago Lying-in Hospital. It appears therefore that favorable results of therapy in a children's hospital can be obtained if the obstetrician is alert to the need for early referral of the affected baby to a pediatic center which can provide prompt treatment of severe cases and chemical and clinical evaluation of the progress of the disease in the milder cases.

ABO Erythroblastosis

The clinical diagnosis of erythroblastosis due to incompatibility in the ABO system differs from that due to the Rh factor largely in the mildness of the signs at birth. The infant affected with A or B erythroblastosis develops jaundice within the first 36 hours of life, and proof of the hemolytic process may or may not be revealed by the hemoglobin level at birth or the development of anemia during the first week of life. The rise in the serum bilirubin levels is slower, but the peak rise may reach the critical level within 36 hours to 5 days of life (Table X). Detection of the jaundice is usually accomplished by an alert nurse.

In 28 infants diagnosed as having A or B erythroblastosis among the babies born at the Chicago Lying-in Hospital during the past 12 years (Table XI) one death occurred in 1945; jaundice developed on the second day of life and deepened during the next 2 days; chemical studies were done in that year; on the third day of life a small transfusion was given because of a mild anemia and progressive icterus, but on the fourth day of life signs of severe encephalopathy developed and the child died; autopsy finding confirmed the clinical diagnosis of kernicterus.

Treatment of the ABO erythroblastosis prior to 1951 consisted of standard transfusion for anemia. Since 1952, the same criteria have been employed for treatment of this type of erythroblastosis as for the Rh type of the disease. In these past 5 years, 22 cases of ABO disease were diagnosed; no deaths have occurred. Exchange transfusions were given to 9 babies, 4 were treated with

TABLE IX. FORTY-SEVEN CASES OF RH ERYTHROBLASTOSIS REFERRED TO BOBS ROBERTS CHILDREN'S HOSPITAL, 1945-1956

YEARS	NO. OF CASES	AGE ON ADMISSION (DAYS)														TREATMENT			NO. OF DEATHS	MORTALITY RATE (%)
		1		2		3		4		5		6-7		10		NONE	SMALL TRANSFUSION	EXCHANGE		
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%					
1945-1951	25	5	20.0	2	8.0	2	8.0	3	12.0	2	8.0	1	4.0	10	40.0	0	23	2	0	0
1952-1956	22	12	54.0	1	4.5	2	9.1	3	13.6	1	4.5	0	--	3	13.0	1	5	16	3	13.6
Total	47																			

TABLE X. ERYTHROBLASTOSIS DUE TO A OR B BLOOD FACTOR IN BABIES BORN AT THE CHICAGO LYING-IN HOSPITAL BETWEEN 1945 AND 1956

YEARS	NUMBER OF CASES	DEATHS		TRANSFUSION THERAPY (NO. OF CASES)					
				NONE		STANDARD		EXCHANGE	
		NO.	%	NO.	%	NO.	%	NO.	%
1945-1952	6	1		1		5		0	
1952-1956	22	0		9		4		9	
Total	28	1	3.5	10	35.8	9	32.1	9	32.1

TABLE XI. BILIRUBIN LEVELS THROUGHOUT THE FIRST WEEK OF LIFE IN INFANTS WITH ABO ERYTHROBLASTOSIS DELIVERED AT THE CHICAGO LYING-IN HOSPITAL 1945-1956

CASE	INCOMPATIBILITY	HEMOGLOBIN (GM. %)				BILIRUBIN LEVELS (MG. %)								TREATMENT	AGE AT TRANSFUSION
		FIRST SIGN OF ICTERUS		FALL		AGE									
		GM.	DAY	HEMOGLOBIN ON SECOND TO EIGHTH DAY (GM.)	DAY (8 DAYS TO 6 WEEKS)	12-35 HOURS	36-48 HOURS	49-60 HOURS	61-72 HOURS	73-96 HOURS	DAY 5	DAY 6	DAY 7-12		
1	A-O	10.2	2			11		8.9						Exchange transfusion	30 hours
2	A-O	15	1						39		23			Exchange transfusion	72 hours
3	A-O	19	2				33	37	7					Exchange transfusion	56 hours
4	A-O	13	3							24.9	20	15	7	Exchange transfusion	96 hours
5	A-O	17	1			14	17	18	22	15		7		Exchange transfusion	72 hours
6	B-O	19	2					35				14		Exchange transfusion	60 hours
7	A-O	20	3			10	12	20		40	25			Exchange transfusion	96 hours
8	B-O	11.8	1	9.3		10			13				5	Standard transfusion	5 hours
9	B-O	15	2	5.6		12		22		21	13			Standard transfusion	16 days
10	A-O	13.5	2	12	9.5	15			29		16			None	--
11	A-O	16	2	12.6			16			18				None	--
12	B-O	16	2	13	10	11		17		18	12			None	--
13	B-O	14	2	12	10.5	13	11							None	--
14	A-O	16	1	14	10.3						17	15		None	--
15	A-O	14	1	13.6	NR	6	10	17	18	14				None	--
16	B-O	14.7	2			11		12						None	--
17	B-O	16.5	2	15	NR	13		19	23	14				None	--
18	A-O	20	1	19	13.4						13		12	None	--
19	B-O	18	1	10.7	11.5	10.9	13.9	19.3						None	--

small transfusions for anemia which developed after the tenth day of life, and 9 did not require treatment. In no cases of ABO erythroblastosis was an exchange transfusion required before the infant was 30 hours old, and in 2 infants the bilirubin levels rose to a critical level of 30 mg. per cent or more only on the fourth day of life at which late time exchange transfusions were given. No infant has required a second exchange.

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CLINICAL VALUE OF SEROLOGIC EXAMINATIONS RELATED TO BLOOD GROUPS IN PREGNANT PATIENTS*†

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THE value of immunohematologic tests in the practice of obstetrics is predicated on three crucial facts:

1. Only by means of such tests can a definitive *diagnosis* of hemolytic diease of the newborn be made.

2. Valuable *prognostic* information may be obtained prenatally as well as neonatally from these tests.

3. Results of these tests frequently influence decisively the selection of *therapeutic* measures.

In view of the rapid developments in the theoretical and technical aspects of this field, this symposium offers a splendid opportunity to raise and answer a number of fundamental questions related to the role of the laboratory in the management of hemolytic disease of the newborn. Are we doing enough tests in order to provide adequate information to the clinician? Or, are we possibly doing too many tests? Are the results of the tests interpreted adequately in order to derive from them the maximum benefit? I hope that this presentation will provide some answers to these questions.

For the purpose of our discussion, I wish to divide immunohematologic tests related to hemolytic disease of the newborn into three categories: (1) routine prenatal tests, (2) routine neonatal tests, and (3) special prenatal and neonatal tests.

Routine Prenatal Tests

Routine prenatal tests are based on the fact that at least 90 per cent of all cases of hemolytic disease of the newborn result from the classical combination of an Rh-negative mother with Rh antibodies bearing an Rh-positive fetus. For practical purposes, we may best define Rh-negative individuals as those who do not have the Rh_0 (D) factor which was the one originally discovered by Landsteiner and Wiener and which still plays the most important role in Rh sensitization. Approximately 15 per cent of the entire population do not possess this factor. Therefore, prenatal testing of every pregnant woman must include determination of the Rh factor. Parenthetically, for practical purposes this should always be combined with determination of the ABO group

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of the expectant mother. Results of the ABO typing will not only be valuable in instances of puerperal hemorrhage, but will also provide preliminary information as to whether there is the possibility of a rarer form of hemolytic disease, namely, that caused by maternal sensitization to the A and B factors. Also, it has been clearly established that the combination of ABO groups in mother and infant has a definite bearing on the likelihood of maternal sensitization to the Rh factor. This aspect will be discussed more fully later on.

All women found to be Rh negative must be tested for the presence of Rh antibodies. Such screening tests can be expected to be necessary in roughly one out of six or seven of all pregnant women. Once Rh antibodies have been demonstrated, their titer must be determined. When a pregnant woman is found to be Rh negative, it is essential to test the Rh type of her husband.

All too frequently omission of this test causes unnecessary concern of patient and physician alike about complications resulting from Rh sensitization. We have seen time and again tests for Rh sensitization repeated through several pregnancies of an Rh-negative woman, until finally her husband was tested and found to be also Rh negative. Needless to say, there need be no further concern with the Rh factor in so wise a mating.

Before a definite conclusion is reached that the husband of an Rh-negative woman is actually Rh negative, however, he must also be tested for the so-called D^u factor, which requires special methods for its detection. Since the D^u factor is capable of causing Rh sensitization, it is obviously important not to miss it, since a husband who is D^u positive, must be considered Rh positive. On the other hand, a woman found to possess the D^u factor should be treated as though she were Rh negative because there is a possibility, though quite remote, of her developing Rh antibodies.

When Rh antibodies have been detected in an expectant mother, we attempt to answer the question as to their significance. In this connection we first try to find out whether or not the fetus carried in the current pregnancy must be Rh positive. This requires information on the zygosity of the husband, that is, as to whether he is homozygous or heterozygous Rh positive. Only when he is homozygous Rh positive, will he transmit the Rh factor to all his children. Serologic tests can provide only presumptive data on the actual genetic make-up of a person, that is, on the basis of the results we can say what the chances are for the person in question to be homozygous or heterozygous Rh positive. Obviously, the predictive value of these odds is limited. More definite information can in some instances be derived from the Rh types of the parents of the husband. In other instances, definite proof of the heterozygosity is furnished by testing of previously born infants, when one of them is found to be Rh negative. Even if the husband of an Rh-negative woman has definitely been established to be heterozygous Rh positive, however, this does not answer the question as to whether the fetus conceived in a particular pregnancy is Rh positive or Rh negative: the chance for either possibility is 50 per cent, regardless of the Rh types of previously born infants.

At this point two important questions should be taken up: when should the first prenatal immunohematologic tests be done? How often and when should they be repeated? We recommend having the first tests done as early as possible, preferably before the end of the first trimester. By means of such early tests we can obtain important information: (1) The presence of Rh antibodies before the end of the third month reflects most likely antibodies carried over from a previous pregnancy or resulting from another form of sensitization, such as blood transfusion; hence such antibodies can be associated with an Rh-negative fetus carried in the current pregnancy. (2) Determination of Rh antibody titer early in gestation offers the best opportunity for

observing a subsequent rise in titer, a finding of considerable prognostic significance, as we will discuss shortly. (3) When absence of Rh antibodies has been established early in pregnancy, subsequent detection of Rh antibodies proves that sensitization took place during the pregnancy under observation, and this in turn is possible only in the presence of an Rh-positive fetus.

Now to the next important question: How often should the immunohematologic tests be repeated during a single pregnancy? Considering first the woman who showed no Rh antibodies when first tested, we recommend repeating the test twice, once at approximately 6 months' gestation and again approximately 4 weeks before the expected date of delivery. What are the reasons for these recommendations? The time of first appearance of antibodies is of paramount importance in connection with their effect on the infant. If antibodies do not appear until the last 4 weeks of gestation, we are fairly certain that they will not cause serious hemolytic disease. On the other hand, clinical disease is much more likely to occur if antibodies have been present for at least 3 months before delivery. Finally, absence of Rh antibodies observed during the early months of pregnancy is likely to induce in the physician a false sense of security if no further tests are done. We have seen several infants born to mothers in whom tests for Rh antibodies were negative in, e.g., the fifth month. Since no further prenatal tests were done, the development of hemolytic disease in the newborn soon after birth was entirely unexpected and this caused delay in the institution of adequate treatment.

In women with Rh antibodies repeat tests are primarily indicated because they may demonstrate a rise in titer. Such a rise, if established convincingly by tests done in the same laboratory at the same time with the same method on the specimens to be compared, is almost definite proof that the fetus carried in this pregnancy is Rh positive. On the other hand, when antibody titers do not essentially change during a particular pregnancy, this in itself does not permit any specific conclusions. Very often this occurs in women who have reached the peak of their antibody production; hence even the presence of an Rh-positive fetus is not capable of stimulating an increase in antibody titer.

There is another benefit to be derived from repeat testing of Rh antibody titers: one can establish with a leeway of from 2 to 4 weeks the length of time during which the infant has been exposed to certain levels of Rh antibodies, especially when the initial titer was rather low. In such cases, it will make a great deal of difference whether a low titer rises to a higher level either 2 weeks or 4 months before delivery. In this connection, it must be admitted that considerable discussion has centered around the question as to whether the height of the titer of Rh antibodies is of prognostic significance, that is, whether it can be evaluated in relation to the presence and severity of hemolytic disease to be expected in the infant. Two opposing views have been expressed: according to one the antibody titer is of no significance at all, whereas according to the other neonatal disease can be predicted with great accuracy from consideration of the antibody titers. In our experience, the truth lies somewhere in between,[1-3] and similar views have been expressed by many expert workers in the field.[4-7] Statistically speaking, high antibody titers, provided that they were present for at least 2 to 3 months of intrauterine life, are associated with diseased infants in the majority of instances, possibly in 80 to 90 per cent. On the other hand, it is true that severe disease may occur in infants born to mothers with consistently low antibody titers, but this is rare, as is the converse event: absence of disease in the infant in the prolonged presence of high-titered maternal antibodies. Thus in general the correlation between height of antibody level and neonatal disease holds true, but we must be aware of the fact that exceptions occur. Hence, we are again dealing, not

with predictions of absolute validity, but rather with odds that can be expressed as 10:1 or 5:1 in favor of presence or absence of disease, as the case may be.

When speaking of titers of Rh antibodies, one must always keep in mind that they are critically dependent on the methods used. While this discussion obviously is not intended to deal with technical aspects of laboratory work, it is necessary to touch upon the question as to whether or not one should use the most sensitive methods for detection of Rh antibodies. Sometimes the opinion is expressed that the use of such methods is of little value, since traces of antibodies detectable only by the most sensitive technique are rarely of clinical significance. On the basis of our experience, we cannot agree with this point of view. For the past 6 years we have used for detection of Rh antibodies what we consider to be the most sensitive technique available at present, namely, red cells treated with the proteolytic enzyme papain. By means of this method we were able to demonstrate the presence of Rh antibodies in a goodly number of cases in which other methods failed to do so. Significantly, follow-up studies on many of these patients furnished proof derived from subsequent tests and the presence of neonatal disease that these early laboratory findings possessed clinical significance.[8]

Reference has been previously made to a relationship between the frequency of Rh sensitization and the combination of ABO groups found in mother, father, and infant. As first pointed out by Levine,[9] and since then amply confirmed by clinical analyses[10] as well as by an experimental approach,[11] Rh-negative women with Rh antibodies are found much more rarely with so-called heterospecific pregnancies than are found in a random population. A heterospecific pregnancy is defined on the basis of the ABO groups of wife and husband, or wife and infant, as a pregnancy in which the wife possesses isoagglutinins anti-A or anti-B reacting with the red cells of her husband and infant. In other words, an Rh-positive fetus whose red cells are incompatible in the ABO group with his mother's blood is less likely to bring about maternal Rh sensitization than is an Rh-positive fetus compatible in the ABO group. The reasons for this peculiar relationship between the ABO group and Rh sensitization are only partly understood.

Let us now summarize the prognostic information as available from prenatal laboratory tests:

1. When an Rh-negative woman has been impregnated by an Rh-positive man, this makes for *potential* hemolytic disease in the offspring.

2. The *likelihood* of Rh sensitization is at least twice as great when the husband's blood is compatible with that of his wife in the ABO group than when this is not the case.

3. Once Rh antibodies are detectable in such an expectant mother, hemolytic disease of the newborn becomes a definite *possibility*.

4. The *probability* of the presence of disease is increased when the husband of a sensitized woman is homozygous Rh positive.

5. A rise in antibody titer during a specific pregnancy is strong evidence for the *Rh positivity* of the fetus.

6. With some exceptions, the *severity of the disease* in the newborn can be expected to be directly proportional to the mathematical product of the height of the antibody titer multiplied by the length of intrauterine exposure of the fetus to the antibodies.

Although not any more belonging to prenatal tests, one more suggestion regarding maternal antibody tests is offered. In all instances, that is, when Rh antibodies were absent as well as when they were present during pregnancy, it

is advisable to repeat the test approximately 2 to 4 weeks after delivery. Whenever Rh antibodies were absent ante partum, the possibility exists that in some women antibodies will develop at that time, for which presumably the entry of fetal blood into the maternal circulation during delivery may be responsible. Obviously, detection of these postpartum antibodies is important for the prognosis of subsequent pregnancies. Similarly, rises in the titer of antibodies present previously are not infrequently observed during the postpartum period. Hence, tests at this time will furnish the most reliable base line for evaluation of antibody titers observed in the next pregnancy.

Routine Neonatal Tests

In view of the subject presented by the next essayist, I intend to make only brief reference to the second category, the routine neonatal tests. Routine examinations should be confined to all infants born to Rh-negative mothers, but they should be done regardless of whether or not maternal Rh-antibodies were detected prenatally. Cord blood should be collected at the birth of such infants, part of it as clotted blood for the serologic tests, and the remainder as heparinized or oxalated specimens to be utilized for hematologic studies. The two strictly immunohematologic tests which must be done routinely are determination of the Rh type and performance of the direct Coombs or antiglobulin test. The first of these tests obviously is crucial: only when the infant is Rh positive can it be affected by the maternal antibodies. A positive Coombs test proves that these antibodies became attached to, or have "coated," the infant's red cells. When negative results were obtained with these two tests, hemolytic disease of the newborn is practically excluded. When they are positive, clinical disease is not necessarily *manifest;* sometimes such results can be associated with *latent* hemolytic disease, which cannot be fully evaluated without hematologic and chemical laboratory tests, and without consideration of the previous obstetric history of the infant's mother.

Special Prenatal and Neonatal Tests

The third category of special prenatal and neonatal tests, is, as a rule, motivated either by the previous obstetric history of the pregnant woman or by abnormal clinical and laboratory findings in the infant. Specific indications are a history of stillbirth or unexplained neonatal death in previous pregnancies, and jaundice or anemia in the infant that cannot be attributed to other definite causes. In all such instances it is certainly worth while to search for evidence of maternal isosensitization, if only for the purpose of excluding this possibility by means of suitable tests. What are these tests? Blood of a pregnant woman, or of a mother of an infant suspected of having hemolytic disease, must be typed for the ABO and Rh factors, including the Rh subtypes, and screened for Rh antibodies. In addition, it is absolutely essential to test the ABO and Rh factors of the husband, and to screen the serum of the woman against the red cells of her husband. If a variety of sensitive methods is used for the latter test, it will almost always be possible to answer the crucial question, namely, whether maternal isosensitization took place to one or the other blood factor present in the husband's but absent in the patient's red cells. What are the blood factors usually implicated? First, there are a number of Rh factors other than the Rh_0 or D previously discussed, which may cause isosensitization of Rh-positive women. Among them the hr′(c) factor is probably most frequently encountered as the cause of hemolytic disease. Then one must consider some of the more rarely involved factors that have been discovered within the last 10 to 15 years, such as Kell, Duffy, Kidd. The clinician need not be concerned

with the specific factor involved, since the clinical manifestations and management are identical with the classic form of the disease caused by Rh sensitization. The only exception concerns selection of blood suitable for treatment of the infant, which is again a responsibility of the laboratory and not of the clinician.

As to neonatal tests, they should include again ABO and Rh typing, and the direct antiglobulin test. The latter test is most important whenever hemolytic disease is suspected: a positive Coombs test is invariably associated with all forms of hemolytic disease, except for that caused by sensitization to the A and B factor. Whenever the previous maternal history has aroused suspicion about isosensitization, cord blood should be collected at birth and used for the tests mentioned as well as for additional hematologic and chemical studies. If the presence of hemolytic disease has not been suspected until after delivery, one must, of course, use peripheral blood for such tests.

AB Sensitization

Discussion of one special causation of hemolytic disease has deliberately been deferred until now: AB sensitization. Diagnosis of this type of hemolytic disease presents special problems because it contrasts with other forms in several ways of which I want to mention three:

1. Prenatal tests have little diagnostic and predictive value as to disease in the newborn.
2. The neonatal direct Coombs test is either negative or only weakly positive.
3. After having given birth to an infant affected with disease, a woman frequently has subsequent infants of the same blood group who are, nevertheless, entirely free of disease.

Thus obviously the usual clinical and laboratory findings are of no avail in establishing or confirming the diagnosis. Hence, in the past the diagnosis was frequently made merely on the basis of finding the difference in ABO group of mother and child, and by excluding other causes of isosensitization. Recent work has improved this situation inasmuch as there are now two tests available that are helpful in neonatal diagnosis. One, proposed by Witebsky[12] several years ago, demonstrates agglutination of the infant's red cells after they have been suspended in a special medium; this apparently represents a specific phenomenon resulting from the coating of the red cells by anti-A or anti-B antibodies. The other test is based on the fact that, in order to affect an infant, maternal antibodies must traverse the placenta and appear in the infant's blood. Hence, it should be possible to demonstrate such incompatible agglutinins in the infant, i.e., anti-A in a baby of group A, or anti-B in a baby of group B. In accord with previous reports and especially the extensive investigation of Zuelzer and Kaplan,[13] we[14] have found that this assumption is valid and can be used as a test helpful in the diagnosis of AB-hemolytic disease. In a series now comprising close to 40 cases of AB-hemolytic disease we have found the incriminated antibody always present in the infant's blood, when suitable techniques were used. However, in about 10 per cent of clinically normal infants this test may be also positive, and hence it can be properly evaluated only when considered together with other laboratory and clinical findings.

Conclusions

The preceding discussion was an attempt to describe in rough outlines the practical tools that are available to the clinician in the form of immunohematologic tests. Development and perfection of these tools undoubtedly would

have been impossible without the active collaboration of the obstetrician and clinician. By the same token the pathologist and immunohematologist hope that adequate utilization and interpretation of these tests will contribute their share toward reaching goals that all of us are aiming for in connection with hemolytic disease of the newborn: improvement in the accuracy of obstetric prognosis; treatment capable of preventing nuclear jaundice; and reduction of perinatal mortality caused by isosensitization.

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FACTORS INFLUENCING PERINATAL MORTALITY IN CESAREAN SECTION

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THE increasing incidence of cesarean section may be attributed to a large extent to its frequent employment primarily in the interest of the infant. This effort to improve the perinatal mortality rate by such intervention demands critical appraisal of the results being obtained. It is of great importance in such an evaluation to determine the risk to the infant which may be related to the operation per se as in the elective or "repeat" section.

The purpose of the present analysis is to ascertain the perinatal mortality in relation to the type of section and the birth weight of the infant. An attempt has been made to assess the risk to the infant due to the operative procedure itself and to the complications of pregnancy or labor which indicated this method of delivery.

Review of the Literature

Gratifying improvement in maternal mortality in patients delivered by cesarean section has occurred. Recent reviews[1, 2] have indicated a mortality rate of 0.3 or 0.4 per cent to 0.05 per cent and several authors[3-6] have reported series of more than 1,000 sections without a maternal death. At Grace-New Haven Community Hospital among more than 1,500 consecutive sections no deaths were encountered. Nevertheless, in view of the nationwide[7] mortality rate of approximately 0.52 per cent, the estimated gross maternal mortality following cesarean section is probably two to four times that associated with vaginal deliveries.

The infant mortality rate has not improved to the same degree as the maternal mortality rate. The Public Health report of 1950[8] shows a gross infant death rate of 43.4 per 1,000 and a neonatal death rate of 20.5 per 1,000 births in the United States. In 1955, the national infant mortality rate[9] was recorded as 26.5 per 1,000 with a neonatal death rate of 19.2 per 1,000 births.

It has been emphasized repeatedly by various authors[10, 11, 12] that the lack of standardization of statistical techniques for reporting fetal deaths makes the comparison of reports from different regions almost impossible. Thus, the perinatal mortality rate as reported from some areas has included all infants weighing over 400 grams while in other vicinities those weighing less than 1,000 or 1,500 grams are eliminated.

A special formula used in New York City is as follows:

$$\frac{\text{Infant deaths (under 1 week) + fetal deaths (28 weeks and over)}}{\text{Live births + fetal deaths (28 weeks and over)}} \times 1{,}000$$

Calculated on this basis, a 19.5 per cent decrease in the perinatal mortality rate occurred during the years 1946 to 1953, with a decline of 12.0 per cent in early neonatal deaths (i.e., under 1 week of age). In 1953, the perinatal mortality rate in New York City was reported to have been 29.7 per 1,000, while in 1955 it had decreased to 20 per 1,000 births. In spite of this and other evidence of improvement in general perinatal mortality rates, it has been asserted that the infant death rate in association with cesarean section has not decreased commensurately.

Material

The material in this study (Table I) includes 571 consecutive cesarean sections performed at the Grace-New Haven Community Hospital between Feb. 16, 1953, and Feb. 16, 1955. Five hundred and seventy-four babies, including 3 sets of twins, were delivered. The cesarean section incidence was 7 per cent of all births in the hospital during this period. The 231 primary and 340 "repeat" sections were done under the supervision and management of qualified members of the General and University staff who have essentially similar policies and techniques. To that extent this review may be considered a controlled clinical study. Indication in 59 per cent of cases was previous cesarean section. Seventy per cent of the primary sections were done for reasons other than cephalopelvic disproportion as determined by roentgen pelvimetry. There were no maternal deaths in this series.

TABLE I. TYPES OF CESAREAN SECTIONS

	NO. OF CASES	%
Primary.—		
Low cervical	214	
Classical	17	
Total	231	41.0
Repeat.—		
Low cervical	319	
Classical	20	
Extraperitoneal	1	
Total	340	59.0

Perinatal Mortality

Vaginal Delivery.—

For the purpose of comparison an analysis was made of the infant mortality associated with vaginal births (Table II) at this hospital during the same period of study. All types of deliveries, including breech and forceps as well as normal spontaneous, were included. This group represents all cases in which no maternal or fetal conditions were present that, in the judgment of the obstetrician, required delivery by section. Among *all* of the 7,487 births by vaginal delivery the stillbirth rate was 1.17 per cent, the neonatal mortality rate was 1.12 per cent, and the total perinatal mortality rate was 2.28 per cent.

Approximately one third of the perinatal deaths involved immature infants weighing less than 1,000 grams. This fact is of very great importance in a consideration of total infant wastage. Failure of these small infants to survive is mainly dependent under present conditions on inadequate development. In this area more benefit can be achieved by the prevention of premature labor

than by selection of a method of delivery. Thus, in comparing the relative influence of different types of delivery on infant mortality it seems more pertinent in this review to exclude these infants. For this reason the corrected* perinatal mortality rate has been calculated to be 1.55 per cent and the corrected† neonatal mortality rate to be 0.71 per cent.

Among the 6,946 mature infants that weighed over 2,500 grams, 33 stillbirths and 9 neonatal deaths occurred. The perinatal mortality rate in this weight group was 0.61 per cent.

TABLE II. PERINATAL MORTALITY BY BIRTH WEIGHT OF 7,487 INFANTS BORN BY VAGINAL DELIVERY

WEIGHT IN GRAMS	TOTAL BIRTHS	STILLBIRTHS	NEONATAL DEATHS	TOTAL DEATHS
Less than 1,000	57	25	31	56
1,001-1,500	55	7	24	31
1,501-2,000	109	11	15	26
2,001-2,500	320	12	4	16
2,501-3,000	1,587	10	7	17
Over 3,000	5,359	23	2	25
Total	7,487	88	83	171

Cesarean Section.—

There were 574 infants delivered by cesarean section with 37 infant deaths (Table III). In the entire group the stillbirth rate was 2.3 per cent, the neonatal mortality rate was 4.2 per cent, and the total perinatal mortality rate was 6.5 per cent. Detailed information concerning individual infant deaths is listed in Tables IV and VI.

TABLE III. PERINATAL MORTALITY BY BIRTH WEIGHT OF 574 INFANTS BORN BY CESAREAN SECTION

WEIGHT IN GRAMS	TOTAL BIRTHS	PRIMARY SECTION		REPEAT SECTION		TOTAL DEATHS
		STILLBIRTHS	NEONATAL	STILLBIRTHS	NEONATAL	
Less than 1,000	5		5			5
1,001-1,500	11	1	5		2	8
1,501-2,000	9		2	2	1	5
2,001-2,500	42		2	1	2	5
2,501-3,000	136	1	1	4	1	7
Over 3,000	371	4	2		1	7
Total	574*	6	17	7	7	37

*Includes twins.

The perinatal mortality, excluding infants weighing less than 1,000 grams, in all types of sections was 5.6 per cent; the neonatal mortality was 2.8 per cent.

Among the 507 infants who weighed more than 2,500 grams delivered by section the perinatal mortality rate was 2.7 per cent. The neonatal mortality in this weight group was 0.8 per cent.

Primary Section.—Among 231 *primary* cesarean sections (Table IV) the stillbirth rate was 2.5 per cent, the neonatal mortality rate was 7.4 per cent, and the total perinatal mortality rate was 9.9 per cent. The perinatal mortality rate of infants weighing more than 1,000 grams was 7.5 per cent and the neonatal mortality rate was 5 per cent.

*Computed as follows: From the total of 171 perinatal deaths there were subtracted the 56 deaths of infants that weighed less than 1,000 grams. The adjusted total of 115 divided by total births minus 57 = 1.55 per cent.

†Computed as follows: From the total of 83 neonatal deaths there were subtracted the 31 neonatal deaths of infants that weighed less than 1,000 grams. Adjusted figure of 52 divided by the number of live births minus 31 = 0.71 per cent.

TABLE IV. CLINICAL CAUSES OF PERINATAL MORTALITY IN PRIMARY SECTION

NO. OF DEATHS		COMPLICATIONS	WEIGHT IN GRAMS
Stillbirths.—			
	6	Central placenta previa	3,640
		Premature separation of placenta	1,215
		Premature separation of placenta	2,500
		Premature separation of placenta, Rh negative	3,250
		Prolonged labor, cephalopelvic disproportion, fetal distress	5,670
		Hydrocephalus, transverse lie	5,760
Neonatal.—			
Less than 1,000 grams	5	Premature separation of placenta, twins	990 and 1,000
		Eclampsia	785
		Severe toxemia	620
		Severe toxemia	830
More than 1,000 grams	12	Placenta previa, fetal distress	1,075
		Placenta previa	1,990
		Placenta previa	2,700
		Placenta previa	4,590
		Premature separation of placenta	1,050
		Premature separation of placenta	1,070
		Premature separation of placenta	1,222
		Premature separation of placenta	1,985
		Premature separation of placenta	2,050
		Severe toxemia, prematurity	1,095
		Prolonged labor, fetal distress	3,175
		Mongolism	2,430

TABLE V. INDICATIONS FOR PRIMARY CESAREAN SECTION

INDICATION	NO. OF CASES	COMPLICATIONS POTENTIALLY UNFAVORABLE FOR INFANT	UNCOMPLICATED
Cephalopelvic disproportion	68		68
Breech	11		11
Fetal distress with trial labor	4	4	
Toxemia	2	2	
Placenta previa	24	24	
Premature separation of placenta	32	32	
Fetal distress	23	23	
Fibroids			
Elderly primipara	6		6
Toxemia	2	2	
Repeated abortion	1		1
Inertia	7		7
Prolonged labor	13	1	12
Cervical stenosis	3		3
Abnormal presentation			
Face	2	2	
Transverse	8	1	7
Compound	1	1	
Previous myomectomy	4		4
Previous vesicovaginal fistula	2		
Diabetes mellitus	3	3	
Toxemia	11	11	
Eclampsia	4	4	2
Total	231	110	121

Six stillbirths occurred. Four were associated with placenta previa or premature separation of the placenta; one with prolonged labor and fetal distress; one with hydrocephalus. One infant weighed 1,215 grams.

Of 17 neonatal deaths, 4 were associated with severe toxemia and 11 with placenta previa or premature separation of the placenta. One death followed a prolonged labor with fetal distress and one mongoloid infant died 12 hours after delivery. Fifteen infants who succumbed weighed less than 2,500 grams, twelve less than 2,000 grams. Five weighed less than 1,000 grams.

The indications for primary section (Table V) in which perinatal death was encountered in this series frequently involved a combination of circumstances urgent for maternal welfare as well as in the interest of the infant despite the factor of prematurity.

Repeat Section.—Among 340 *repeat* cesarean sections (Table VI) the stillbirth rate was 2 per cent, the neonatal mortality rate was 2.1 per cent, and the total perinatal mortality rate was 4.1 per cent births. The corrected* perinatal mortality rate was 3.4 per cent and the neonatal mortality rate was 1.2 per cent.

TABLE VI. CLINICAL CAUSES OF PERINATAL MORTALITY IN REPEAT SECTION

NO. OF DEATHS	COMPLICATIONS	WEIGHT IN GRAMS
Stillbirths.—		
7	Severe erythroblastosis	2,160
	Severe erythroblastosis	3,000
	Premature labor, antepartum death	1,770
	Ruptured uterus	2,500
	Ruptured uterus	2,500
	Ruptured uterus	2,790
	Antepartum death	
Neonatal.—		1,770
7	Placenta previa	1,180
	Premature separation, atelectasis	2,290
	Premature labor, severe erythroblastosis	2,925
	Premature labor, breech, congenital heart disease	2,050
	Anencephaly, prematurity	1,202
	Hyaline membrane disease, prematurity	1,830
	Mongolism, fetal distress	3,400

TABLE VII. COMPLICATIONS IN REPEAT SECTIONS

COMPLICATIONS	NO. CASES
Placenta previa	3
Premature separation of placenta	6
Premature labor	8
Ruptured uterus	3
Hematoma of broad ligament	1
Defective scar	2
Abnormal presentation	4
Multiple pregnancy	2
Erythroblastosis	11
Congenital defects	3
Medical disease	6
Total	49

There were 7 stillbirths. Three stillbirths accompanied rupture of the scar of a previous section. Two infants had severe erythroblastosis. Two were born dead prematurely and weighed less than 2,000 grams.

There were 7 neonatal deaths. Two were associated with placenta previa or premature separation of the placenta. Three premature infants had anencephaly, congenital heart lesions, and pulmonary hyaline membrane disease. One Mongoloid infant died 8 hours after delivery. One infant had severe erythroblastosis. Eight of the infants weighed less than 2,500 grams; 3 weighed less than 2,000 grams.

*Ruptured uteri not included.

The high incidence of complications present in this group of patients who had cesarean sections (Table VII) resulted in a perinatal mortality rate nearly twice that of vaginal delivery. However, only 2 infants who weighed more than 2,500 grams died. Both had major congenital defects. Having had a previous section gives no assurance against pregnancy wastage from accidents of gestation, congenital maldevelopment, or serious medical complications involving the fetus. Avoidance of the premature onset of labor necessitating prompt delivery represents an obvious factor by which fetal mortality in this group might have been reduced. Bleeding in the second trimester from placental complications made early cesarean section imperative with delivery of 2 premature infants that might have survived at term. Rupture of the scar of classical incisions, each following 2 previous sections, represents a well-known hazard which accounted for 3 intrapartum deaths. Greater attention to factors influencing healing of the uterine wound and a more prevalent use of lower segment incisions may aid in minimizing the catastrophic ruptures.

Classification of Cases According to Presence or Absence of Complications.—The 571 cesarean sections in this series were divided into two categories (Table VIII): Group I, those cases in which no known maternal or fetal complications were present that might affect infant survival, and Group II, in which such complications involving the mother or infant were present.

TABLE VIII. PERINATAL MORTALITY IN CESAREAN SECTION IN RELATION TO COMPLICATIONS INVOLVING THE INFANT

NO. OF CASES		STILLBIRTHS	NEONATAL DEATHS	TOTAL DEATHS
Group I (Uncomplicated).—				
Primary	121	0	0	0
Repeat	301	0	0	0
Total	422	0	0	0
Group II (Complicated).—				
Primary	110	6	17*	23
Repeat	39	7	7	14
Total	149	13	24	37

*Five weighed less than 1,000 grams.

Group I: 422 infants (422 sections) were delivered by cesarean section *without* an infant death.

Group II: 152 infants (149 sections) were delivered by section with 13 stillbirths and 24 neonatal deaths.

Of the 13 stillbirths, 4 were associated with vaginal hemorrhage, 3 with severe erythroblastosis fetalis, 3 with rupture of the uterine scar, 2 with the premature onset of labor, one with hydrocephalus, and one with prolonged labor. Four infants weighed less than 2,500 grams.

Of 24 neonatal deaths, 13 were associated with hemorrhage, 4 infants had congenital lesions, one had erythroblastosis fetalis, and one infant (1,830 grams) had pulmonary hyaline membrane disease. Four deaths were associated with toxemia and one with prolonged labor and fetal distress. Five infants weighed less than 1,000 grams, 19 less than 2,500 grams.

The perinatal mortality rate in section *when complications were present* (Group II) was 20.0 per cent. The neonatal mortality rate was 11.0 per cent. A portion of this high mortality is unavoidable when there is severe fetal maldevelopment. In the presence of other influencing factors, it is possible that better results may be obtained as methods of management improve.

No infant deaths were encountered in 422 cesarean sections (Group I in this series) in which no known factors were present which might have endangered the infant. This lends support to the opinion, noted by others, that the operation per se adds little so-called inherent risk when conducted under

well-controlled conditions. A pediatrician or other experienced person should be in attendance to give active care to the newborn who may have respiratory difficulty. All obstetricians are aware of the occasional infant who fails to intitiate normal respiratory exchange promptly and may later present findings of hyaline membrane disease. It is our practice to transfer all infants who weigh less than 2,500 grams to an incubator in the premature nursery where constant supervision is available.

The role of anesthesia and the value of employing proper anesthetic technique have been recently emphasized by Taylor,[13] Lund,[14] and others.[15]

The perinatal mortality rate in Group II reflects the fact that complications often make cesarean section imperative in the interest of the mother and at the same time jeopardize the infant. It is in this group of patients, also, that cesarean section must be most judiciously used in our attempt to decrease the over-all perinatal mortality. In our present series, complications of a serious nature were present in 39 of 340 "repeat" and 110 of 231 primary sections. Included in these were 56 patients with placental bleeding, 34 instances of fetal distress, and 31 instances of major complicating medical disease. The difficult problem of lowering the high fetal mortality rate when these conditions are present is apparent from our further analysis. Only 2 neonatal deaths appear to have been preventable. One followed prolonged labor with fetal distress and one (the infant weighed 1,830 grams) was caused by hyaline membrane disease.

Complications.—

Vaginal bleeding: Antepartum hemorrhage predominated as a serious accident of pregnancy. A significant degree of vaginal bleeding in the third trimester occurred in 64 cases (Table IX), or an incidence of 11 per cent of all section patients. Cesarean section was performed in most instances when intervention was deemed urgent because the degree of hemorrhage endangered the mother or when there was evidence of fetal distress. In premature separation of the placenta, hysterotomy was elected when the nature of the cervix was unfavorable for vaginal delivery and when it was thought that further delay would jeopardize the infant. Careful observation of the fetal heart for evidence of distress is important. Absence of fetal heart sounds, as determined by the usual auscultatory methods, is not always reliable evidence of fetal death in utero in abruptio placentae.

TABLE IX. INCIDENCE OF CESAREAN SECTION FOR HEMORRHAGE

NO. SECTIONS	COMPLICATIONS		% INCIDENCE
Primary.—			
231	Placenta previa	20	8.7
	Premature separation of placenta	35	15.1
	Total	55	23.8
Repeat.—			
340	Placenta previa	3	0.9
	Premature separation of placenta	6	1.8
	Total	9	2.7

TABLE X. OUTCOME OF INFANTS IN SECTION FOR HEMORRHAGE

WEIGHT IN GRAMS	NO. LIVED	NO. DIED
Less than 1,000	0	2*
1,001-1,500	0	6
1,501-2,000	3	2
2,001-2,500	10	2
Over 2,500	34	5
Total	47	17

*Twins.

Forty per cent of all perinatal deaths of infants in this study delivered by cesarean section were associated with hemorrhage (Table X). Of these 17 infants who died, 12 (or 70 per cent) weighed less than 2,500 grams; 8 weighed less than 2,000 grams. The total perinatal mortality rate in sections complicated by bleeding in this series among infants weighing more than 2,500 grams was 12.5 per cent. Among infants weighing less than 2,500 grams it was 48 per cent.

Placenta previa or premature separation of the placenta occurred in 55 (or 23.8 per cent) of 231 *primary* sections. There were 15 infant deaths including 4 stillbirths. Ten of these infants weighed less than 2,500 grams. The total perinatal mortality rate was 26 per cent.

Hemorrhage occurred in 9 (or 2.7 per cent) of 340 patients who had *repeat* sections. Two infants died; each weighed less than 2,500 grams. The total perinatal mortality rate was 22.2 per cent.

McNeill[16] has noted a 40 per cent perinatal loss due to asphyxia from bleeding complications. There was a 39.3 per cent infant mortality rate with premature separation and a 23.8 per cent loss with placenta previa. Bysshe[17] in an earlier report found 45.4 per cent fetal loss in cesarean section performed for hemorrhage.

It has been our policy to delay section in placenta previa with the patient under close observation with blood replacement, when bleeding is slight and impairment of fetal circulation is inconsiderable, until fetal maturity can be established. Despite this principle, section was required in eight (35 per cent) of the cases when the infant weighed less than 2,500 grams. Eastman[18] has commented that "about 25 per cent of these patients lend themselves to expectant treatment while 25 per cent require immediate treatment if lives are to be saved."

Much of the improvement in the reduction of fetal loss in abruptio placentae has been credited by Landesman[19] to speedier decision to evacuate the uterus and in placenta previa to earlier recognition with institution of protective measures to achieve fetal maturity before operative intervention.

We are of the opinion that, even in instances involving the premature infants, improved fetal outcome will follow prompt section particularly when minimal evidence of fetal distress is evident. Anoxia secondary to disturbed placental circulation may result in mental impairment. Fuldner[20] and Latham, Anderson, and Eastman[21] have called attention to the high coincidence of premature separation and cerebral palsy. For these reasons we believe that if infants are to be saved, close observation of all patients with vaginal bleeding must be carried out, with prompt decision for intervention without delay, particularly if changes in fetal heart sounds or other signs of fetal distress occur.

TABLE XI. CLINICAL FINDINGS IN FETAL DISTRESS

FINDINGS	NO. CASES
Abnormal fetal heart rate or rhythm	32
Meconium-stained amniotic fluid	14
Cord complications	13
Tetanic contractions	6
Bandl's ring	1
Prolonged labor	6
Premature separation of placenta	8
Erythroblastosis	1
Recent virus infection	1
No pathologic lesion found	6

Fetal distress: Cesarean section was performed primarily on the basis of signs of fetal distress in 34 cases (Table XI), or 0.4 per cent of all deliveries. As might be expected, the incidence of fetal distress varies widely in different

hospitals. In this study the criteria used most commonly in the diagnosis were applied, namely: (1) changes in rate, rhythm, and quality of fetal heart sounds on auscultation, (2) presence in vertex presentation of meconium in amniotic fluid, and (3) change in activity of the infant. Slowing of the fetal heart rate below 100 per minute with no sustained improvement following administration of oxygen to the mother was felt to be of greater significance. The inadequacy of these relatively crude means of diagnosis is readily apparent. At present, intensive investigation of electronic methods of continuous observation of the fetal heart as an aid to earlier detection of distress is being conducted in the Department of Obstetrics in an effort to elucidate this problem.

In the group with this complication the perinatal mortality consisted of one stillbirth and 2 neonatal deaths (or 8.8 per cent). One infant weighed 1,075 grams, in a case of placenta previa and profuse vaginal bleeding. Another infant (3,175 grams) died 1½ hours after section for distress during a prolonged labor. One stillborn infant (5,670 grams) was delivered by section after prolonged labor of a multipara with unrecognized cephalopelvic disproportion.

The incidence of cesarean section for fetal distress in our series (0.4 per cent) compares favorably with that of McCall and Fulsher,[22] who found section indicated in 45 of 8,785 deliveries. They encountered 5 neonatal deaths (or 8 per cent). Landesman[19] has reported an infant loss of 8.75 per cent in 46 abdominal deliveries for fetal distress among 567 sections.

It is our belief that active intervention in this group undoubtedly resulted in the salvage of a number of infants who would have otherwise succumbed to serious damage from the effects of anoxia.

Prematurity: Six hundred and eight (or 7.5 per cent) of all newborn in this study weighed less than 2,500 grams and were classified as premature (Table XII). In the entire group there were 152 deaths with a total perinatal mortality rate of 25 per cent. Among premature infants weighing more than 1,000 grams the mortality rate was 17 per cent.

TABLE XII. PERINATAL MORTALITY OF PREMATURE INFANTS

METHOD OF DELIVERY	NO. OF BIRTHS	NO. OF DEATHS		
		STILLBIRTHS	NEONATAL	TOTAL
Vaginal	541	55	74	129
Cesarean section:				
Primary	43	1	14	15
Repeat	24	3	5	8
Total	608*	59	93	152

*Includes all infants weighing less than 2,500 grams.

There were 484 infants delivered vaginally that weighed between 1,000 and 2,500 grams. Seventy-three deaths, including 30 stillbirths, occurred, with a perinatal loss of 15 per cent. The neonatal mortality rate was 10 per cent and varied almost directly with the birth weight (Table XIII).

TABLE XIII. NEONATAL* MORTALITY OF PREMATURES BY WEIGHT

WEIGHT IN GRAMS	VAGINAL DELIVERY			CESAREAN SECTION		
	TOTAL	LIVED	DIED	TOTAL	LIVED	DIED
1,000-1,500	48	24	24	10	3	7
1,501-2,000	98	83	15	7	4	3
2,001-2,500	308	304	4	41	37	4
Total	454	411	43	58	44	14

*Liveborn infants only.

Sixty-two infants weighing between 1,000 and 2,500 grams were delivered by section. There were 18 infant deaths with a perinatal loss of 29 per cent. The neonatal mortality rate was 18 per cent. Although the neonatal mortality rate in cesarean section births in this weight group was greater than that encountered in vaginal delivery, it is evident that fatal outcome in cesarean section was preceded almost always by ominous insults to fetal physiology. Of 58 liveborn premature infants in this group, 56 were exposed to additional factors hazardous for the infant. Nine deaths followed section for vaginal hemorrhage. One 1,095 gram infant succumbed after section for severe toxemia; 3 had congenital defects. One neonatal death, that of an 1,830 gram infant with pulmonary hyaline membrane disease, followed repeat section for premature onset of labor. Despite the frequent combination of unfavorable circumstances, 44, or 75 per cent, of the liveborn prematures survived.

Prematurity offers serious perils for the newborn. It seems probable also from our review that the increase in mortality risk in section involving premature infants is mainly dependent on the nature and severity of other coexisting contributory factors.

Comment

The trend toward wider use of cesarean section is based on the postulate that, at least in pathologic entities productive of anoxia or when the use of traumatizing forceps is anticipated, the prognosis for the infant might be improved. Paradoxically, numerous reports have appeared in the literature calling attention to the high perinatal mortality in cesarean section. In the identification of which patients will benefit by abdominal delivery, mature clinical judgment continues to be of great importance. It has been felt that a detailed review of the results of cesarean section, to be compared with those obtained in vaginal delivery, should aid in the selection of the method of delivery which offers the most favorable prognosis for the infant.

In this series 422 uncomplicated sections were performed with no infant deaths. While the number of cases observed does not permit definitive conclusions, our findings indicate that the "repeat," or elective, section per se offers little risk for the infant. This is an important consideration in instances when vaginal delivery after previous section is contemplated.

In the group of patients who had cesarean sections in whom complications definitely deleterious for the infant were present, the perinatal mortality rate of 20 per cent reflects the influence of such factors as placental bleeding, congenital anomalies, and prematurity, which have been analyzed further in this report.

Antepartum hemorrhage was associated with 40 per cent of all perinatal deaths in section. Mortality among infants weighing over 2,500 grams was reduced to 12.5 per cent in the presence of this serious complication.

Prematurity plays a major role. More than 60 per cent of the perinatal deaths in cesarean section delivery and 75 per cent in vaginal delivery involved infants weighing less than 2,500 grams. When section was performed for fetal distress, 92 per cent of the infants survived.

It is hoped that improved methods of prevention and management of these major factors affecting perinatal mortality will be developed. Timely intervention with delivery by section for such complications as hemorrhage and/or

fetal distress may favor the chance of survival of either the premature or full-term infant. Adequate facilities for pediatric care of the newborn are essential to obtain best results.

Summary

Infant mortality associated with 571 consecutive sections and 7,487 vaginal deliveries has been reviewed. The perinatal mortality rate in section among infants who weighed more than 1,000 grams was 5.6 per cent. Although the rate was 3½ times that in vaginal delivery in this series, the *combined* section and vaginal delivery perinatal mortality rate of only 1.8 per cent was accomplished.

No infant deaths were encountered in 422 sections when complications endangering the fetus were absent. Section, per se, should not add to infant mortality.

Among premature infants delivered by section, 75 per cent survived in spite of the presence of additional complications of pregnancy or labor.

Factors contributing to perinatal mortality have been discussed.

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CURRENT ASPECTS OF CESAREAN SECTION AND PERINATAL MORTALITY

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THE medical literature is filled with articles about cesarean section, but there are still many problems associated with this operation that remain unanswerable and promote lively discussion in medical circles. These problems involve not so much operative techniques, as in former days, but the various factors contributing to infant loss. They cannot be answered except by evaluation of large, accurately documented current series. It seems of little use to evaluate cases from the distant past, for new techniques, particularly in the fields of support, infection, and anesthesia, have radically changed the potentialities of abdominal delivery.

Material

The material in this study is comprised of work performed in the years 1950 to 1955, inclusive, and was obtained from the "Obstetrical Statistical Cooperative." The data were thus obtained from ten hospitals most of which are affiliated with medical schools. As for previous reports,[1, 2] these data have been gathered under uniformly specified conditions and constitute a sample sufficiently large and recent to yield much pertinent information. There was a total of 85,556 single deliveries, of which 3,816 were by cesarean section, an incidence of 4.46 per cent. There were 1,597 secondary and 2,219 primary operations with frequency rates of 1.86 per cent and 2.59 per cent, respectively (Table I).

Table I. Sources of Material

Hospital	No. Deliveries	Cesarean Sections	
		No.	%
University of Maryland			
University Hospital	15,953	640	4.0
Mt. Sinai, Baltimore	15,456	494	3.2
Mt. Sinai, N. Y. C.	11,147	683	6.1
Beth El, Brooklyn	4,937	248	5.0
University of Colorado	3,676	84	2.3
Johns Hopkins	2,622	152	5.8
State University of N. Y.			
Kings County	18,444	803	4.4
Long Island College	8,514	470	5.5
Maimonides	3,379	203	6.0
Cumberland	1,428	39	2.7
Total	85,556	3,816	4.46
Incidence of primary cesarean section			2.59
Incidence of repeat cesarean section			1.86

There are vast differences between repeat and primary section. These include not only the maternal factors of indications and morbidity but, equally important, they involve questions of perinatal prognosis. Therefore, these two groups will be considered separately.

The distribution of the cases according to race is shown in Table II. It is well recognized that the gross over-all perinatal loss among Negroes is considerably greater than among white patients, although, once born alive, the risk is less for offspring of the former. The increased loss among Negroes is related to the high prematurity rate and a propensity to accidents of pregnancy. These factors are to a large extent eliminated when cesarean section is done for the indication of previous abdominal delivery and in this group the loss rates for Negroes and whites are similar. However, in primary section, where the indication is frequently just such an accident, the total loss rate is higher and some difference appears between the two races (Table III).

TABLE II. DISTRIBUTION OF CESAREAN SECTION BY RACE

RACE	PREVIOUS SECTION		PRIMARY SECTION	
	NO.	%	NO.	%
White	1,141	71.5	1,459	65.8
Negro	440	27.5	743	33.5
Others	16	1.0	17	0.7
Total	1,597	100.0	2,219	100.0

TABLE III. PERINATAL LOSS ACCORDING TO RACE

RACE	PERINATAL LOSS			
	PREVIOUS CESAREAN SECTION		PRIMARY CESAREAN SECTION	
	NO.	%	NO.	%
White	34	2.9	121	8.3*
Negro	13	2.9	77	10.4*
Others	0		1	5.8
Total	47	2.9	199	9.0

*P = .38.

Indications

The indications for the primary cesarean sections are listed in Table IV. The incidences of the different indications are in keeping with those in recently reported series. Dystocia (contracted pelvis, inertia, large baby, and pelvic tumors), toxemia, and hemorrhage accounted for 64.8 per cent of all the primary cesarean sections. Delivery of diabetic mothers by cesarean section has become more popular in recent years as indicated by the fact that it ranks seventh in importance in this series. Among the 85,556 deliveries there were 428 cases of diabetes; 25 per cent of these patients were delivered abdominally.

Rh Incompatibility as an Indication for Cesarean Section.—There were 157 patients who had repeat cesarean sections and were Rh negative but in only one of these cases was the operation performed because of Rh incompatibility. In the primary cesarean group, there were 209 Rh-negative patients and in 11, 5.3 per cent, the operation was performed because of Rh incompatibility.

These figures do not give the true incidence of cesarean section as a method of delivery for patients who have Rh incompatibility, but they do indicate that this complication was not a frequent indication for cesarean section. The use of section in the face of rising antibody titers in order to limit the exposure of the infant to antibodies is still a controversial point. The work of Lathe[3] indicating why the premature infant fails to excrete bilirubin seems to militate

against this indication. However, preterm but not premature delivery, as recently reported by Evans,[4] may be of value in certain cases of Rh incompatibility and, in such instances, section may be performed if induction of labor is not feasible or successful.

TABLE IV. INDICATIONS FOR PRIMARY CESAREAN SECTION

INDICATION	NUMBER	%
Cephalopelvic disproportion	477	21.5
Inertia	307	13.8
Large baby	77	3.5
Pelvic tumors	27	1.2
Toxemia	226	10.2
Placenta previa	165	7.4
Premature separation of placenta	160	7.2
Malpresentation	158	7.1
Diabetes	107	4.8
Elderly primipara	99	4.5
Fetal distress	89	4.0
Prolapse of cord	52	2.3
Bad obstetrical history	27	1.2
Previous vaginal plastic operation	20	0.9
Others	228	10.4
Total	2,219	100.0

Perinatal Loss

Abnormal Presentation and Perinatal Loss.—It is well known that certain abnormal presentations, particularly brow and transverse lie, have a high associated perinatal loss when delivery is vaginal. Therefore, many of these patients with abnormal presentations are delivered by cesarean section. In this study there were 456 patients in the primary cesarean group who had presentations other than vertex. However, in only 34.4 per cent of these abnormal presentations was cesarean section done because of the abnormal presentation. In the remainder the operation was performed because of other complications of which the two most frequent were antepartum hemorrhage, 18.2 per cent, and contracted pelvis, 13.6 per cent.

TABLE V. PERINATAL LOSS ACCORDING TO PRESENTATION

	PREVIOUS CESAREAN SECTION			PRIMARY CESAREAN SECTION		
	TOTAL CASES	LOSS		TOTAL CASES	LOSS	
		NO.	%		NO.	%
Vertex	1,398	30	2.1	1,643	124	7.5
Breech	88	7	7.9	249	33	13.2
Face	4	0	—	25	0	—
Brow	0	0	—	21	0	—
Compound	3	1	33.3	9	0	—
Transverse lie	22	1	4.5	138	19	13.7

TABLE VI. PERINATAL LOSS. ABNORMAL PRESENTATION ONLY INDICATION FOR CESAREAN SECTION

	PREVIOUS CESAREAN SECTION			PRIMARY CESAREAN SECTION		
	TOTAL CASES	PERINATAL LOSS		TOTAL CASES	PERINATAL LOSS	
		NO.	%		NO.	%
Breech	1	0	0.0	40	0	0.0
Face	0	0	0.0	15	0	0.0
Brow	0	0	0.0	14	0	0.0
Compound	0	0	0.0	4	0	0.0
Transverse lie	3	0	0.0	84	8	9.5

TABLE VII. PERINATAL LOSS ACCORDING TO TYPE OF OPERATION

OPERATION	PREVIOUS CESAREAN SECTION			PRIMARY CESAREAN SECTION		
	TOTAL CASES	LOSS		TOTAL CASES	LOSS	
		NO.	%		NO.	%
Classical	167	12	7.2	248	46	18.5
Elective	129	5	3.8	182	43	23.6
Labor	38	7	18.4	66	3	4.5
Low flap	1,365	28	2.0	1,854	131	7.1
Elective	1,111	19	1.7	874	80	9.2
After labor	254	9	3.5	980	51	5.2
Extraperitoneal	6	1	16.6	64	5	7.8
Elective	5	1	20.0	8	2	25.0
After labor	1	0	—	56	3	5.4
Cesarean hysterectomy	59	6	11.1	53	17	32.1
Elective	50	4	8.0	36	10	27.9
After labor	9	2	22.2	17	7	41.1

TABLE VIII. PERINATAL LOSS AS RELATED TO ANESTHESIA. ELECTIVE REPEAT CESAREAN SECTION

TYPE OF ANESTHESIA	PREMATURE			MATURE			COMBINED		
	TOTAL CASES	PERINATAL MORTALITY		TOTAL CASES	PERINATAL MORTALITY		TOTAL CASES	PERINATAL MORTALITY	
		NO. CASES	%		NO. CASES	%		NO. CASES	%
Transplacental	14	2	14.3	104	1	1.0	118	3	2.5
Conduction	73	13	17.8	814	8	1.0	887	21	2.5
Both	36	9	25.0	374	3	0.8	410	12	2.9
Unknown	0	0	0	3	0	0	3	0	0
Total	123	24	19.5	1,295	12	0.9	1,418	36	2.5

The procedure of cesarean section in the presence of an abnormal presentation does not in itself assure a live baby (Table V). The main reason is the association of other complications which jeopardize the infant. However, there was no perinatal loss associated with cesarean sections performed for abnormal presentations only except transverse lie and even there it was less than the overall loss associated with this presentation (Table VI).

Types of Operation and Perinatal Mortality.—The types of operation and their respective perinatal mortality are listed in Table VII. In the entire series, low flap cesarean section was performed in 84.3 per cent of the cases with a perinatal mortality of 4.9 per cent. Classical cesarean section was performed in 10.9 per cent with a perinatal mortality of 13.9 per cent. There are several possible explanations for the increased perinatal loss in the classical group, one of which is the choice of this type of operation by many operators in certain acute complications, particularly placenta previa where the fetus may be already jeopardized.

The extraperitoneal type of cesarean was performed in only 1.8 per cent of the cases. This reflects the recent trend away from this complicated operation.

Cesarean hysterectomy was performed 112 times, an incidence of 2.9 per cent, with a perinatal mortality of 20.5 per cent. In the repeat group sterilization was the indication for the hysterectomy in 76.3 per cent of the cases and rupture of the uterus in 16.9 per cent. The indications for this procedure in the primary cesarean sections were varied but the two most common were uncontrollable uterine bleeding and sterilization. It is interesting to note that intrapartum infection played practically no role in the decision to perform a cesarean hysterectomy.

If the elective classical cesarean sections are compared with the elective low flap sections, there is a significant increase in perinatal loss in the classical group.

Type of Anesthesia and Perinatal Mortality.—In order to evaluate the effect of anesthesia on perinatal mortality it is necessary to eliminate, as far as possible, other factors which might adversely influence the perinatal mortality. Therefore, only the patients who had elective repeat cesarean sections were selected. The results of this appraisal are given in Table VIII. It can be seen at once that in the mature group (infants over 2,500 grams) there is no difference among the different types of anesthesia. In the premature group, although there are variations in the perinatal mortality rates among the types of anesthesia, these are not statistically significant. Irving[6] in 1945, Hellman[8] in 1953, and Hingson and Hellman[9] in 1956 stated that the type of anesthesia did not affect the perinatal mortality in mature infants. Hellman showed that this was also true for premature infants but Irving contended that conduction anesthesia was preferable for prematures. Most operators have followed Irving's suggestion, but these data seem to substantiate the viewpoint of Hellman. It is far more important to have a capable anesthesiologist than to specify a certain type of anesthesia.

There were 123 patients in the elective repeat group who had premature infants. This is an incidence of 8.6 per cent and reflects to some extent the problem of judging fetal weight even when this is done by experts. This problem will be discussed in greater detail later in the paper.

Labor Complications.—The complications of labor and the related perinatal losses are listed in Table IX. There is a fairly high perinatal loss associated with placenta previa and premature separation of the placenta. Many of these cesareans were performed in the interest of the mother and many of the infants were premature. These perinatal losses were compatible with other modern

figures. From this study, no statement is possible as to the role of cesarean section in the treatment of these complications but certainly abdominal delivery does not assure a live infant.

TABLE IX. PERINATAL LOSS RELATED TO LABOR COMPLICATIONS

	PREVIOUS CESAREAN SECTION			PRIMARY CESAREAN SECTION		
	TOTAL CASES	LOSS		TOTAL CASES	LOSS	
		NO.	%		NO.	%
Placenta previa, total	9	0	—	126	13	10.3
Placenta previa, partial	11	1	9.1	118	15	12.7
Placenta, low implanted	5	0	—	27	3	11.1
Premature separation, partial	14	5	35.7	163	57	34.9
Premature separation, total	17	3	17.6	13	13	100.0
Rupture of marginal sinus	1	1	100.0	7	1	14.3
Other antepartum hemorrhage	17	2	11.7	31	4	12.9
Prolapse of cord	0	-	—	67	4	5.9
Rupture of uterus	30	3	10.0	2	2	100.0
Primary uterine inertia	4	1	25.0	155	9	5.8
Secondary uterine inertia	8	0	—	324	15	4.6

The perinatal loss associated with prolapse of the cord is quite small and reflects the satisfactory results that can be obtained by cesarean section in this complication when the cases are individualized.

Rupture of the uterus occurred 32 times, 30 times in cases of previous section and twice in cases of primary cesarean. This is an incidence of 0.1 per cent in the primary cesarean section group and 1.9 per cent in the repeat cesarean section group. The 2 ruptures of the uterus in the primary cesarean group followed long labors associated with dystocia problems and both infants died. Cesarean hysterectomies were done in both cases.

There were 3 infants lost perinatally in the 30 cases of ruptured cesarean section scars, and all were in patients who had had previous classical cesareans.

There were 155 patients who developed primary uterine inertia and had a primary cesarean section. The indication for the cesarean was uterine dysfunction in 56.1 per cent and contracted pelvis in 27.7 per cent of these. There were 9 perinatal deaths.

Pitocin stimulation was given to 32 patients who were then delivered by cesarean section. These cases represent failures of stimulation therapy. The perinatal mortality in this group of "Pitocin failures," eliminating fetal deaths prior to labor, was 6.3 per cent, as compared to a 3.3 per cent loss in the patients operated upon for the same indication without Pitocin. These percentages are not significantly different nor do they differ from an over-all perinatal loss of 3.9 per cent in Pitocin failure recently reported by Hellman, Kohl and Schechter.[1]

The high incidence of contracted pelvis associated with uterine dysfunction should be emphasized for frequently the abnormal type of labor is the first indication of the more serious underlying complication. If this possibility is considered early in labor, proper investigative steps can be taken and the injudicious use of Pitocin stimulation avoided.

Perinatal Loss According to Infant Weight.—This aspect of the study has been divided into a primary cesarean section group and a previous cesarean section group (Table X). The gross perinatal loss in the primary group was 9.0 per cent. If deaths prior to labor are disregarded, however, the loss was 6.3 per cent. The 20.1 per cent incidence of prematurity is so high because of the

large number of patients on whom cesarean section was done for bleeding disturbances, toxemia, and diabetes. These three complications accounted for 61.3 per cent of all the primary cesareans in patients who were not in labor. The perinatal loss for mature infants was 4.2 per cent but, eliminating deaths prior to labor, the loss was 2.5 per cent.

As would be expected, the perinatal loss in all categories in the repeat group was much lower. The gross perinatal mortality of 2.9 per cent is lowered only to 2.5 per cent if deaths prior to labor are not included and in the mature group there is no change.

TABLE X. PERINATAL LOSS ACCORDING TO WEIGHT

WEIGHT (GRAMS)	TOTAL CASES	ALIVE	PERINATAL MORTALITY			
			DIED PRIOR TO LABOR	DIED DURING LABOR	NEONATAL DEATH	MORTALITY %
Primary Cesarean Section.—						
Less than 400	1	0	1			100.0
401-1,000	35	3	8	1	23	91.4
1,001-1,500	65	41	3		21	36.9
1,501-2,000	126	83	12	3	28	34.1
2,001-2,500	220	195	11	1	13	11.4
2,501-3,000	456	435	7	5	9	4.6
3,001-3,500	651	634	6	5	6	2.6
3,501-4,000	461	445	2	4	10	3.5
4,001-4,500	152	146	1	2	3	3.9
4,501-5,000	32	29	2	1		9.4
Over 5,000	10	9	1			10.0
Unknown	10	0	5	2	3	100.0
Total	2,219	2,020	59	24	116	9.0
1,001-2,500						22.4
Over 2,500						4.2
Incidence of prematurity						20.1
Previous Cesarean Section.—						
Less than 400	0					
401-1,000	4	0		1	3	100.0
1,001-1,500	10	5	2		3	50.0
1,501-2,000	24	16	3		5	33.3
2,001-2,500	144	131	2		11	9.0
2,501-3,000	448	440	1		7	1.8
3,001-3,500	641	640			1	0.2
3,501-4,000	258	254			4	1.6
4,001-4,500	59	59				0
4,501-5,000	5	5				0
Over 5,000	0					
Unknown	4	0		2	2	100.0
Total	1,597	1,550	8	3	36	2.9
1,001-2,500						14.6
Over 2,500						1.2
Incidence of prematurity						11.4

It has been accepted for a long time that one of the main reasons for the perinatal mortality associated with repeat cesarean section is prematurity. This is seen in Table X where the incidence of prematurity is 11.4 per cent with a perinatal loss in this group of 14.6 per cent. One explanation for the high incidence of prematurity is the inability to judge accurately the weight of the fetus and thus the too early performance of the cesarean section. To overcome this objection, some people allow the patient to go into spontaneous labor and then perform the operation, believing that the incidence of prematurity and its associated perinatal loss would be reduced.

In an effort to determine the validity of the above, an analysis of the repeat cesarean group was made. There were 1,418 elective repeat cesarean sections.

There were only 1,172 patients of this group, however, who did not have some associated condition which might have, even remotely, contributed to the perinatal loss. These 1,172 patients, therefore, constitute a completely uncomplicated group of elective repeat cesarean sections. There were 956 of these patients who had no labor and the incidence of prematurity was 7.2 per cent and a total perinatal loss of 1.2 per cent. There were 121 patients who were delivered of mature infants by repeat cesarean sections following the onset of labor with a perinatal loss of 1.6 per cent. There is no significant difference between these two perinatal loss rates and it seems from this appraisal that in the uncomplicated case it makes no difference whether or not the repeat cesarean section is done electively prior to labor or after the onset of labor.

Thirty-nine infants that weighed between 400 and 1,000 grams were born by cesarean section. Bleeding complications or toxemia were the indications in 82 per cent of these cases; 8 per cent of the sections were done on previous section patients who went into labor.

The most frequent cause of death in the infants was hypoxia, often associated with atelectasis and less frequently with pneumonia. Many of the deaths of premature infants were attributed to prematurity without any specific organic lesion. Malformations incompatible with life accounted for 4.8 per cent of the perinatal mortality.

Comment

Although there has been a broadening of the indications for cesarean section in recent years, the incidence has not changed appreciably. Moreover, the incidence at any particular institution must be appraised separately for primary and repeat cesarean sections for it may well be higher in an institution committed to the policy of "once a cesarean, always a cesarean."

Cesarean section is not the solution for all obstetric problems. This method of delivery, contrary to the opinions of many of the laity and medical profession alike, does not guarantee a normal live baby. As has been shown in this paper, there is a marked perinatal loss often due to the complication that is the indication for the cesarean section. However, there is at least a 1 per cent perinatal loss in the uncomplicated elective repeat section. This is the same as in uncomplicated vaginal delivery of term infants. This raises the question whether or not there should be more selection of previous cesarean patients for elective vaginal delivery. It is almost impossible to foretell which previous cesarean scars will rupture, and if rupture does occur there is a 10 per cent perinatal loss. This high perinatal mortality seems to point to the advisability of preventing the catastrophe of rupture of the uterus by performing routine repeat cesarean sections. However, when the cases are analyzed, it is found that all the perinatal loss occurred in the thirty-sixth to thirty-seventh week of gestation which is usually much earlier than most workers would do an elective routine repeat cesarean section. It is suggested, therefore, that this aspect of cesarean section receive more study. This may possibly lead to agreement with Schmitz[11] that "once a cesarean section, not necessarily always a cesarean section."

It has been shown that rupture of a previous cesarean section scar may follow either classical or low flap types and that these ruptures may occur prior to or after the onset of labor in both types. It appears, however, that the rupture of a previous classical scar is much more serious for the life of the fetus since all of the perinatal loss in this series was in such cases.

The complications of labor of abnormal presentation and prolapse of the umbilical cord are not in themselves indications for cesarean section. Rather, each case must be carefully considered and individualized in an effort to determine which method of delivery is most likely to assure a live baby and an undamaged mother.

Summary

1. A study of 3,816 cesarean sections, 2,219 primary and 1,597 repeat, has been presented.

2. The gross perinatal mortality in the primary group was 9.0 per cent, and 2.9 per cent in the repeat group. Eliminating deaths prior to labor, these figures are corrected to 6.3 and 2.5 per cent, respectively. The perinatal mortality in mature infants, corrected by eliminating deaths prior to labor, was 2.5 per cent in the primary and 0.9 per cent in the repeat cesarean sections.

3. The type of anesthesia is not an important factor in the cause of perinatal mortality.

4. In the uncomplicated elective repeat cesarean section, the perinatal loss was not affected by performance of the section prior to rather than at the onset of labor.

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TOTAL HYSTERECTOMY FOR STERILIZATION FOLLOWING CESAREAN SECTION

A Report of 65 Cases

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THE purpose of this study is to consider further the advisability of elective prophylactic total hysterectomy at the time of cesarean section when a patient is to be sterilized. This procedure seems to be a logical development in preventive obstetrics and gynecology. Elective or early cesarean section has become a safe operation in our present-day well-equipped and well-staffed hospitals. Elective prophylactic cesarean section subtotal hysterectomy has also proved to be safe and relatively easy. Just as total hysterectomy in the nonpregnant patient has replaced the subtotal operation to prevent benign or malignant disease of the cervix, it is felt that indicated prophylactic total hysterectomy at the time of cesarean section in selected cases is an acceptable procedure.

The usual criteria for sterilization in this community are followed. It is generally accepted that with the third cesarean the request of both the patient and her husband for sterilization is reasonable because of the hazards of pregnancy in a scarred uterus. In special cases, with additional indications and with older patients, sterilization requested at the time of the first or second cesarean section is allowed. All cases are individualized. Sterilization is usually discouraged. The serious nature of rupture of the scarred uterus in subsequent pregnancy is the basis for the policy of elective repeat cesarean section and is the indication for sterilization when requested. It is important to inform the patient of this possibility and acquaint her with the nature of sterilization.

If a patient is to be sterilized, it is explained to her that the procedure has no effect on the glands or the sex life or on the time of the menopause. The patient is told that if circumstances are favorable and she is to be sterilized, it is desirable to remove the uterus in order to prevent any subsequent uterine disease. The patient should understand that menstruation is not a necessity and that the only purpose of the uterus is to hold a pregnancy. The advantages to the patient of eliminating all future uterine disease are apparent. Randall and Gerhardt stated that almost 4 per cent of women over 20 years old will develop cancer of the uterus at some time in their life. In view of the substantial potential for subsequent uterine disease, hysterectomy as a routine

procedure is justified if it can be demonstrated to be relatively safe. This study of 65 cesarean section total hysterectomies is presented for further evaluation of this procedure.

History

Professor Porro of Pavia, Italy, performed the first successful cesarean section subtotal hysterectomy and bilateral salpingo-oophorectomy in 1876 to remove a badly infected uterus. Subsequently the operation was modified to preserve the tubes and ovaries, making it a more acceptable procedure. Indications were soon extended to include hemorrhage, rupture of the uterus, tumors, and sterilization. In 1941, Reis and De Costa reviewed 636 cases of cesarean section hysterectomy and stated, "Cesarean hysterectomy is not difficult. In elective cesarean hysterectomy, the morbidity and mortality should not exceed that of simple hysterectomy." They reported 54 cases with no deaths. Dieckmann, Bjork, and Aragan reported 153 cases over a 15 year period in 1948 with one death from peritonitis in 1937 of a 239 pound, toxemic, infected, diabetic patient. These are cases of the subtotal operation.

The high incidence of cancer and infection of the cervical stump and the demonstrated safety of the total abdominal hysterectomy at the time of cesarean section suggested that the more extensive operation may be preferable. Davis in 1951 reported a series of 100 cases with acceptable results and felt justified in recommending total hysterectomy as a routine procedure for sterilization. Subsequent reports by Dyer and associates, Bradbury, and Siegel recommend that total hysterectomy replace the subtotal in the hands of the trained obstetrician.

Analysis of Material

These sixty-five cesarean section total hysterectomies were done at The Kaiser Foundation Hospitals from 1947 to 1957. All were elective, prophylactic procedures for uterine disease or indicated sterilization. Postpartum hysterectomies are not included, nor are subtotal hysterectomies. Sterilization is not regarded as an indication for cesarean section. The incidence of cesarean sections has varied between 4 and 5 per cent annually, with over 50 per cent repeat cesarean sections. These 65 operations were done by 15 different surgeons. Extensive myomectomy, previously ruptured uterus, and hysterotomy were regarded as indications for cesarean section.

TABLE I. AGE AND PARITY OF 65 PATIENTS

PARITY	TOTAL	AGE				
		20-24	25-29	30-34	35-39	40-44
0	0	0	0	0	0	0
i	13	0	2	2	6	3
ii	38	5	15	13	3	2
iii	7	0	3	3	1	0
iv	4	0	0	3	1	0
v	2	0	1	0	0	1
viii	1	0	0	0	1	0
Total	65	5	21	21	12	6

The age of the patients, as shown in Table I, is a factor in the consideration of sterilization, but if the patient is to be sterilized, hysterectomy is elected regardless of the patient's age. Sixty of the 65 patients were over 25 years of age. The 5 patients under 25 years were having their third cesarean section; one of the 5 was a juvenile diabetic.

The indications for cesarean section total hysterectomy are shown in Table II. Thirty-five patients were having their third cesarean section. Nineteen patients were undergoing a second cesarean section and had other indications, such as high parity, extensive uterine scarring, and myomas. The 11 patients who had primary cesarean sections were sterilized in most cases for serious medical or surgical complications. They were in an older age group and 9 of the 11 had three or more children.

TABLE II. INDICATIONS FOR STERILIZATION

Third cesarean section		35
Second cesarean section		19
Indications:		
Myomas	3	
Extensive myomectomy	2	
Ruptured uterus	2	
Dehiscence, old scar	4	
Diabetes	1	
Constitutional inferiority	1	
Para iii or more	6	
First cesarean section		11
Indications:		
1. Age 26, para iii, gravida vi	Menometrorrhagia, myomas, deep thrombophlebitis	
2. Age 35, para iii, gravida iv	Old rupture of uterus and bladder, vesicovaginal fistula	
3. Age 35, para ii, gravida iv	Old Spinelli operation	
4. Age 37, para ii, gravida iii	Obstructive myoma, face presentation	
5. Age 39, para viii, gravida ix	Central placenta previa, multiparity	
6. Age 31, para iii, gravida iv	Three colporrhaphies for old third-degree tear	
7. Age 44, para i, gravida ii	Essential hypertension, 240/140, with toxemia. Fibroids	
8. Age 30, para ii, gravida iii	Intestinal obstruction. Incidental cesarean section. Fibroids	
9. Age 31, para iv, gravida v	Previous pelvic thrombophlebitis, twice with pulmonary embolus. Cephalopelvic disproportion, with membranes ruptured 54 hours, 16 hour labor	
10. Age 38, para i, gravida iii	Chronic pyelonephritis with bilateral renal calculi, multiple fibroids	
11. Age 44, para v, gravida vi	Frank breech. Uterine inertia. Membranes ruptured 3 days	

Technique

Maturity of the fetus is confirmed by x-ray. Two units of blood are crossmatched. The abdomen is opened through a longitudinal or horizontal incision. A bladder flap of visceral peritoneum is dissected from the lower uterine segment. The bladder is often intimately adherent to the site of the previous cesarean section incisions in the uterus. The dissection of the bladder from the uterus is often difficult and bloody. A longitudinal incision is made in the uterus, and the baby delivered. The patient is given intravenous Methergine and intrauterine Pitocin, and the placenta delivered. Hemostasis can usually be obtained by closing the uterine incision with towel clips.

The round ligaments are clamped, cut, and ligated. The uteroovarian and broad ligaments are clamped close to the uterus, cut, and ligated. The uterine vessels are clamped, cut, and doubly ligated after the uterus is firmly contracted. It is usually desirable to clamp, cut, and ligate the uterosacral ligaments separately. The cardinal ligaments are clamped with Heaney clamps, cut, and ligated. Traction on the cervix through the uterine incision makes it easier to enter the vaginal vault and complete the amputation of the uterus.

The lateral vaginal fornices are obliterated with a stitch which approximates the uterosacral and cardinal ligaments and so-called uterovesical fascia on each side. An over-and-over circular continuous stitch in the vaginal mucosa from the inside out, around the circumference of the vaginal vault gives hemostasis and draws together the apex of the vault like a purse string. This is left open to drain the area beneath the bladder flap. Meticulous hemostasis is important.

Morbidity and Complications

The incidence of febrile morbidity was 4.6 per cent. Antibiotics were given prophylactically to all but 7 patients. Blood transfusions were given to 47 patients as shown in Table III to correct anemia and replace lost blood. The patient who received 2,500 c.c. of blood received 2 units before operation. The bladder was perforated in three cases during the attempt to dissect it from the lower uterine segment where it was intimately adherent to the site of the previous scar. Two of these patients had had previous extraperitoneal cesarean sections, presumptive evidence of intrapartum infection. There were 2 pelvic hematomas which were absorbed without drainage and with no sequelae.

TABLE III. TRANSFUSIONS

NUMBER OF C.C.	NUMBER OF PATIENTS
500	32
1,000	9
1,500	4
2,000	1
2,500	1

Incidental Surgery and Pathological Conditions of the Uterus

Table IV lists the incidental operations which consisted mainly of management of the appendix. Inversion of the entire appendix into the cecum is the method of choice as it eliminates any possibility of infection. This procedure consists of ligation of the mesoappendix which is then stripped from its serosal attachments to the appendx. If the entire appendix is patent, the appendix can be inverted into itself and into the cecum from the tip. If the distal portion is obliterated, the inversion can be accomplished by commencing the intussusception at the base of the appendix. A hemostatic nonabsorbable stitch is placed at the base of the appendix in the wall of the cecum at the attachment of the mesoappendix to hold the taenia coli with a purse string and maintain the intussusception.

TABLE IV. INCIDENTAL SURGERY

Appendectomy	3
Inversion of appendix	15
Inversion of appendix and resection of ovary	1
Inversion of appendix and repair of umbilical hernia	1
Inversion of appendix and repair of bladder laceration	3
Bilateral salpingo-oophorectomy	1
Right salpingo-oophorectomy	2
Excision of Meckel's diverticulum and inversion of appendix	1
Excision of tumor, right side of neck (cystic lymphoma)	1
Excision of vesicovaginal fistula	1
Lysis of adhesions causing intestinal obstruction	1
Ligation of vena cava and repair of evisceration	1

The patient with a vesicovaginal fistula from a previously ruptured bladder and uterus had a hysterectomy to facilitate the repair of the fistula. The patient had an uneventful recovery and went home on the seventh day.

The defects in the lower uterine segment and occult ruptures of the uterus were obscured by the new uterine incision and were not reported by the pathologist, as shown in Table V. The rupture listed was not in an old scar but was at the cornu of the uterus.

TABLE V. PATHOLOGICAL CONDITIONS IN THE UTERUS

Fibroids	10
Spontaneous rupture	1
Subserosal hemorrhage	1
Total	12

Comment

The removal of the uterus at the time of cesarean section differs from the usual total abdominal hysterectomy in the increased vascularity and the adherence of the bladder to the uterine scars of the previous operations. The procedure is often easier than total hysterectomy with a nonpregnant uterus in the hands of a skilled surgeon. It is more difficult when the cervix is dilated, and when there are dense adhesions from the previous operations. Exposure is excellent as the elasticity of the vagina allows delivery of the uterus with ease. The tissues are friable and must be handled gently. Meticulous hemostasis is important to prevent bladder flap and broad ligament hematomas (2 cases). Should the bladder be entered, it should be closed in two layers with a retention catheter left in for 5 days.

Care must be exercised to see that the uterus is well contracted prior to removal, as a considerable amount of blood can be removed with the uterus.

The favorable postpartum convalescence of these patients is impressive. The clinical course is usually as good as, or better than, that following the ordinary cesarean section. The follow-up on these patients has been good. To date, no ovarian disease has developed. There has been no dyspareunia or reported adverse effect on the patients' sex function.

Summary

A series of 65 consecutive elective cesarean section total hysterectomies is analyzed. Hysterectomy is elected when sterilization is recommended and indicated. This procedure has no harmful aftermath and protects the patient from subsequent uterine disease. Blood loss, bladder injury, and pelvic hematomas are the principal complications.

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VAGINAL DELIVERY FOLLOWING CESAREAN SECTION

Management of the Parturient With a Uterine Scar

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THE incidence of cesarean section has steadily increased,[5, 7, 8, 10, 21, 24] and the operation is often resorted to for the termination of almost any obstetric problem. This opinion was voiced in 1916-1917, by Williams,[30] Mason,[17] and others.[31] Has the widened use of the operation led to abuse? We believe it has; so do many others.[8, 26, 27, 28, 32] Certainly, cesarean section is done too frequently for questionable or invalid indications. It is often the quick and easy way out for the obstetrician and relieves the anxieties of the patient's family and her physician.

A few of the "indications" for section in the patients whom we subsequently delivered from below were: "one month overdue," "failure to dilate," "hemorrhage following excision of tumor of the vagina," "hysterotomy for dead six month infant," "rectoperineal fistula," "venereal warts," "fear of disruption of scar from appendectomy done at eight months' gestation," "inguinal hernia," "deep transverse arrest," "arcuate uterus," "acute appendicitis."

Many authors[4, 6, 15, 22, 23] believe that the obstetrician who favors a trial of labor in patients who have had a cesarean section for an indication no longer present assumes less maternal risk than if he does repeat sections routinely. The reported incidence of uterine tear following previous classic sections is less than 4 per cent. Elton[13] reported 1.5 per cent; Brierton[3] 3 per cent; Kerr[16] 4 per cent; and Audebert[1] 6 per cent. In low cervical scars the incidence is much lower,[2, 14, 29] about one-sixteenth that of the classical operation. Eastman[12] thinks the over-all rate is 2 per cent or less. Of the 2 to 4 per cent who would incur rupture of the uterus, about 11 per cent would die.[9] In routine repeat section the mortality according to Skeel and Jordan[25] would be 1 to 2 per cent. Schneider[24] gave the rate as 0.816 per cent, almost double the mortality from uterine rupture which is less than 0.44 per cent. The improvements in anesthesia, surgical techniques, administration of blood, antibiotics, and control of electrolyte and fluid balance result in better healing and a consequent decrease in the frequency of rupture and, of course, these same factors lower the mortality rate of cesarean section and the mortality in patients who incur rupture of the scar whether before or after the onset of labor.

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Management

We make every effort to determine the type of section, the indication, and the postoperative course. The patients are followed by the Chief of the Obstetric Section. About two weeks from term, x-ray pelvimetry by the Pickhardt-Dippel-Simpson technique is done and the case is presented to the staff. If clinical and x-ray pelvimetry indicate an adequate pelvis and there were no complications following the patient's previous section, we usually decide upon vaginal delivery. We explain the problem to the patient and point out that the reason for her previous cesarean section is no longer present. We also point out the risks and do not minimize them. If her former obstetrician has thoroughly convinced her that all subsequent deliveries *must be* abdominal, we do not argue the point.

The patients are brought to the hospital one week prior to the expected date of confinement and kept until delivery. An occasional patient enters the hospital in premature labor. As soon as the patient is admitted, her blood is cross-matched and 1,000 c.c. of blood is kept on call until after delivery. Labor and delivery are conducted as in other patients except that they are watched more closely. The membranes are ruptured relatively early to speed up labor. Caudal anesthesia is started as soon as labor is well established. After delivery the Chief of the Obstetric Section explores the uterus to determine the status of the scar and to decide whether the uterus is competent for future pregnancy and vaginal delivery.

Clinical Material

From Jan. 1, 1948, to Dec. 31, 1956, 222 of our prenatal patients gave a history of cesarean section or hysterotomy. We elected to do repeat sections on 109 of these patients and delivered 113 by the normal route. One of these was delivered 3 times and 10 were delivered twice, a total of 125 vaginal deliveries yielding 127 infants.

TABLE I. GENERAL STATISTICAL DATA, JAN. 1, 1948, TO DEC. 31, 1956

Number of mothers delivered		19,586	
Number of deliveries		19,764	
Number of multiparas		10.079	
Number with history of cesarean section		222	2.13%
Number of cesarean sections performed		159	0.81%
Primary	50	0.25%	
Repeat	109	0.56%	

TABLE II. TYPE OF OPERATION PRECEDING VAGINAL DELIVERY

Low cervical section	56
Classic section	38
Unknown	11
Extraperitoneal	3
Lacerated uterus, cause undetermined	1
Hysterotomy	4
Total	113

One hundred and two of the 113 patients had apparently had an uneventful postoperative convalescence. Eight were febrile; one had pneumonia, one thrombophlebitis, one a breast abscess, one a hematoma of the broad ligament, 3 had stitch abscesses, one pyelitis, and 2 had severe postpartum toxemia.

Eighty-six patients had not had a previous vaginal delivery and were considered to have "nulliparous birth canals," 18 had vaginal delivery prior to

the original section and 8 had vaginal deliveries subsequent to original section and before delivery here. Five in the "nulliparous" and 5 in the parous group had had 2 cesarean sections before delivery here. One had had 3 cesarean sections and one had had 4.

TABLE III. INDICATION FOR ORIGINAL OPERATION

Disproportion	36
Prolonged labor	11
Placenta previa	27
Abruptio placentae	7
Breech	9
Toxemia	8
Miscellaneous	14
Unknown	1

Thirty-five of our patients had undergone cesarean section because of "disproportion." In 12 the disproportion was due to a "large fetus," in 12 due to a "small pelvis," in 5 due to unfavorable fetal position or presentation, and in 6 the cause of the disproportion was not clear. Twenty-one of these women (2 in the "excessively large baby" group, 10 in the "small pelvis" group, 3 in the "malposition" group, and 6 in the "unclear" group) were delivered vaginally of a fetus as large as or larger than the baby born by section.

Twenty-two of the patients were more than 30 years old and well over half of these had "nulliparous birth canals," never having been delivered from below.

In 103 cases we were able to determine the location of the placenta by the Pickhardt-Dippel-Simpson x-ray pelvimetry technique. Implantation was anterior in 71 cases and posterior in 32. Nine of the 12 poor scars were associated with anterior implantation.

Results

In 107 deliveries the onset of labor was spontaneous. Labor was induced by amniotomy in 17; 6 of these were given "Pitocin drip" intravenously.

TABLE IV. METHOD OF DELIVERY AND ANESTHESIA

METHOD OF DELIVERY		ANESTHESIA	
Spontaneous	16	Caudal	117
Low forceps	104	Low spinal	3
(includes 17 rotations)		Trilene and local	1
Breech delivery	7	No anesthesia	4
	127*		125†

*Includes 2 sets of twins.
†All but 11 had episiotomy.

TABLE V. LENGTH OF LABOR

	NUMBER OF CASES	"PAROUS" CERVIX	"NULLIPAROUS" CERVIX
Under 2 hours	4	4	0
2-8 hours	58	29	29
8-12 hours	24	5	19
12-16 hours	13	3	10
16-20 hours	5	1	4
20-24 hours	7	0	7
25 hours and over	14	3	11
	125	45	80

The shortest labor was 1 hour, 15 minutes. The longest labor, recorded as 65 hours, was very desultory and the time of onset of labor was questionable.

Of the 125 women delivered, 90 were found to have had good scars and 12 poor scars. One, a low cervical scar, ruptured. All 12 of the poor scars were from the classical operation. In 22 patients the examination either was not done or not recorded.

Morbidity and Complications.—There was no maternal death. Puerperal morbidity by standard definition occurred in 6 cases: one from ruptured uterus for which a hysterorrhaphy was done; one from an allergic reaction to blood transfusion; one from a common cold; one from mild endometritis; and 2 unexplained.

TABLE VI. COMPLICATIONS OF VAGINAL DELIVERY

Pre-eclampsia	2
Premature separation of placenta	4
Manual removal of placenta	3
Laceration of cervix*	6
Separation of episiotomy	4
Rupture of uterus	1
Hemorrhage, atonic	2

*Three associated with forceps rotation.

During this period we had 5 cases of rupture of the uterus: one occult rupture found at repeat section, 2 patients admitted from other hospitals with rupture before the onset of labor, one in a gravida vi with no uterine scar, and one (described below) whom we delivered per vaginam.

The single case in which rupture of the uterus occurred may be reported in some detail.

This 19-year-old patient had had a classical cesarean section at the age of 14 because she was a "victim of rape, very young and immature, appearing even younger than the age given." She was admitted at term complaining of gradually increasing constant pain in both lower quadrants and flanks. The blood pressure was 128/74 with a pulse rate of 88. The uterus was almost tetanic. There was no tenderness over the cesarean scar. The cervix was well effaced, one finger tip dilated, and the vertex at station 0. The fetal heart rate was slow and irregular and a short while later it could not be heard. A tentative diagnosis of abruptio placentae was made, and she was taken to the delivery room for a sterile vaginal examination. The membranes were ruptured. The fetal heartbeat again became audible but was irregular and could not be heard two hours after admission. The blood pressure stayed normal, but the pulse rate increased gradually to 140. Labor progressed normally. After 11 hours of labor she was delivered easily by forceps rotation from right occipitotransverse to occipitoanterior presentation. The stillborn infant weighed 3,204 grams. The placenta was delivered three minutes later and had an old blood clot over about one-third of the surface. Upon exploration of the uterine cavity a laceration of the anterior wall was found. A hysterorrhaphy was done under caudal anesthesia. She has since been delivered at term by cesarean section and the operator could not find the uterine scar.

The attitude of the patients of this method of management was interesting. Many volunteered that they preferred normal delivery. The preference of the others was found by direct questioning. One hundred and eight preferred vaginal delivery, 4 were uncertain, and one definitely preferred cesarean section.

The perinatal mortality was 7.1 per cent compared to the over-all clinic rate of 2.2 per cent. There were 7 stillbirths and 2 neonatal deaths. If we exclude 2 late abortions (fetuses weighing 553 grams and 730 grams), the rate is 5.0 per cent. One intrapartum death (Case 6, Table VII), due to rupture of the uterus, probably would have been avoided if we had done a cesarean section in

advance of labor. This is the only fetal death that can be attributed directly to the method of delivery. In fact, 3 cases were selected for vaginal delivery because the fetuses were small and had died before labor.

TABLE VII. PERINATAL MORTALITY

1. Neonatal death	Male, 2,750 grams. Died at 96 hours. Autopsy, bronchopneumonia
2. Stillbirth	Male, 552.8 grams
3. Stillbirth	Female, 730 grams. Premature separation of placenta
4. Stillbirth	Male, 1,162.3 grams. Antepartum death. Autopsy, cause undetermined.
5. Stillbirth	Male, 2,268 grams. No fetal movements for one week.
6. Stillbirth	Male, 3,203.5 grams, 55.9 cm. Ruptured uterus
7. Stillbirth	Female, 3,359.4 grams, 53.3 cm. Antepartum death. Partial premature separation of placenta
8. Stillbirth	Female, 1,772 grams. Severe diabetes
9. Neonatal death	Female, 2,892 grams. Died on fifth day with *E. coli* meningitis; membranes ruptured 36 hours before labor; *E. coli* amnionitis treated heavily with antibiotics

Comment

Our series is too small to warrant positive statements, but we believe we are following sound practice. There has been no maternal mortality either in those delivered vaginally following a previous section or in those upon whom we did a repeat section. There is no difference in morbidity, and the perinatal death rate is essentially the same. We lost one infant by electing delivery from below.

We do not believe that a uterine scar dooms a woman to cesarean section in every subsequent pregnancy. Perhaps the majority can be delivered more safely by the vaginal route. The candidates for vaginal delivery must be carefully selected and supervised by a competent obstetrician in a well-equipped hospital ready to meet all emergencies. We do not feel as secure as McLane,[18] who said, "In this service, a delivery through the normal birth canal after a cesarean section is seen so frequently as scarcely to be a matter of remark." We are aware of the risk, so aptly characterized by Nattrass,[20] who said, "The perversity of fate will still ordain that some patients in whom all the circumstances appear impeccable shall undergo uterine rupture even before labor begins." Possibly with each additional pregnancy the probability of rupture increases, although Duffy[11] reported upon one patient whom he delivered normally 9 times following a section for placenta previa. The patient who has been delivered normally three times here developed a thinning of the scar to the point that we advised her to have no more pregnancies.

A commonly held concept is that the risk of rupture of the uterus increases according to the number of previous sections. That is, that two scars would be twice as likely to rupture as one, and that three scars would be three times as likely, etc.[12] McNally and Fitzpatrick,[19] however, report an incidence of uterine rupture through the old scar in 1.5 per cent of 130 cases with a history of four or more cesarean sections. Of our 12 patients with a history of multiple sections, 8 had good scars upon uterine exploration and 4 had poor scars. None incurred rupture.

Factors which favor delivery by the normal route are: a vaginal delivery before the section, an uncomplicated postoperative course following the section, a low cervical section, early "fixing" of the presenting part, a "ripe" cervix, and a good mental attitude on the part of the patient.

Conclusions

In a well-equipped and well-staffed hospital, vaginal delivery following cesarean section done for a temporary indication is a rational procedure not "fraught with danger." It can be accomplished with low mortality and morbidity rates, and good fetal salvage in carefully selected cases.

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HYPOFIBRINOGENEMIA AND THE PLACENTA*

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SEVERAL discussions of hypofibrinogenemia in pregnancy have appeared in the recent literature.[1-13] It has been generally agreed that a deficiency in the plasma fibrinogen may accompany cases of severe abruptio placentae, intrauterine retention of a dead fetus, and amniotic fluid embolism. The result is a coagulation defect with hemorrhagic manifestations.

Many features of the physiopathological processes of fibrinogen depletion are not yet understood. Likewise, there is a certain amount of controversy concerning the clinical management of these patients.

We have had occasion to observe 6 patients with hypofibrinogenemia associated with pregnancy. Four of these were associated with a dead fetus, one of which cases was actually a missed abortion. Two patients had hypofibrinogenemia in connection with abruptio placentae.

It is the scope of this paper to report our experiences in the 6 cases we have observed, and to suggest another concept of the actual mechanics of defibrination. We[14] have presented this concept in more detail in a recent report.

Case Reports

CASE 1.—Mrs. C. E. B. This 25-year-old para ii, gravida iii, whose estimated date of confinement was May 20, 1954, entered the hospital on May 7, 1954, for observation and study because of ecchymoses which occurred on the arms and legs 3 days before. Intrauterine fetal death had occurred approximately 12 weeks before admission. No other bleeding manifestations were present. The patient was Rh isosensitized and had high antibody titers. Her previous pregnancy terminated at 8 months' gestation with delivery of a stillborn infant.

Laboratory studies on admission showed the plasma fibrinogen level to be 80 mg. per cent; the Schneider[9] fibrin assay titer 1:10, control 1:200.

An attempt was made to restore the fibrinogen level with 1,500 c.c. of fresh plasma; following this, however, the fibrinogen level was only 90 mg. per cent; the fibrin assay titer was 1:50.

Four grams of commercial fibrinogen (Parenogen) was then given. The fibrin assay titer was elevated to 1:400. The pregnancy was immediately terminated by a subtotal hysterectomy. A transfusion of 500 c.c. of whole blood was given prophylactically during the operative procedure. No unusual bleeding was encountered. The fibrin assay titer immediately after operation and 12 hours postoperatively was 1:400; on the fifth postoperative day it was 1:800, and the fibrinogen level was 430 mg. per cent. The patient had an uneventful postoperative course and was discharged in good condition on the eighth postoperative day.

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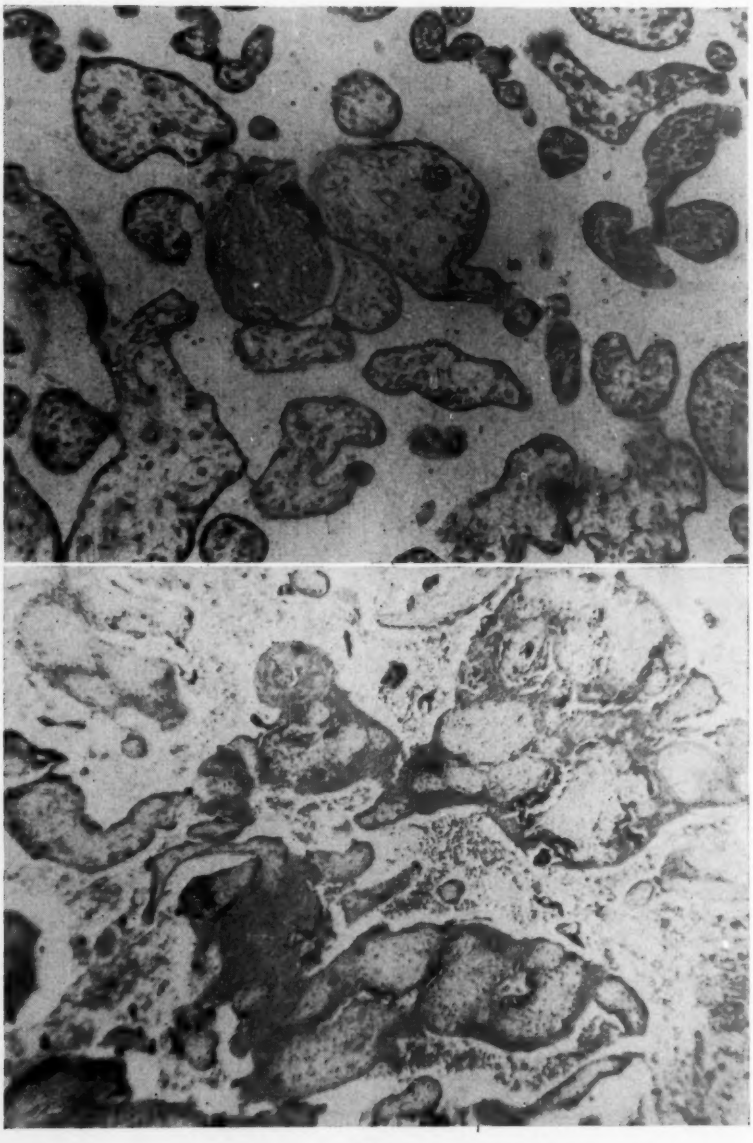
Study of the placenta showed a very extensive deposition of fibrin. Some of this fibrin was in conjunction with a massive infarct occupying about one third of the placental mass. In other portions there was a considerable amount of intervillous fibrin formation (Fig. 1, *A* and *B*).

A.



B.

Fig. 1.—*A*, Histologic appearance of a normal placenta at term, showing a single thrombus of fibrin on the surface of a villus. These thrombi may be found in any normal placenta. This illustration is shown for comparison with *B*.

***B*, Histologic appearance of placenta from patient with dead fetus in utero showing extensive intervillous fibrin thrombosis. Villi are surrounded by fibrin; however, the intervillous spaces remain patent, thus permitting circulation of maternal blood. (From Ashworth and Stouffer: Am. J. Clin. Path. 26: 1031, 1956.)**

Comment.—This case was encountered at the time when there were only 12 cases of hypofibrinogenemia associated with intrauterine retention of a dead fetus found in the literature, and only 3 of these were diagnosed before the onset of labor. In view of this paucity

of information, this patient was subjected to a hysterectomy after elevation of the fibrinogen level to normal. This was done, rather than to risk induction of labor which at the time was associated with too many unknown possible hemorrhagic complications. Likewise, at this time, hysterotomy was considered unwise, as mentioned by Reid and associates,[7] because of possible contamination of the abdominal cavity. With present-day knowledge, induction of labor or hysterotomy would be considered the treatment of choice in terminating this pregnancy.

CASE 2.—Mrs. G. E. C. This 28-year-old para ii, gravida iii, was admitted to the hospital on Dec. 24, 1954, approximately 8 weeks from term, because of a sudden gush of vaginal bleeding. This was followed by intense abdominal pain with superimposed uterine contractions.

Physical examination revealed a boardlike, firm, tender uterus. The fetal heart tones were not heard. The cervix was firm and admitted one finger tip. The patient was observed for 3 hours. During this time vaginal bleeding was slight, but the cervix did not change. The abdominal pain and contractions continued. Her blood pressure remained within normal limits but the pulse showed a steady rise to 112. A blood count shortly after admission showed: erythrocyte count 3.39 million, hemoglobin 8.2 grams, hematocrit 23 volumes per cent, leukocyte count 17,000. Five hundred cubic centimeters of whole blood was immediately started.

A low cervical cesarean section was then done and a premature stillborn infant was delivered. A large clot approximately 3 inches in diameter was found behind the placenta. No unusual bleeding was noted in the uterine cavity or musculature. One cubic centimeter of Pitocin was injected into the uterine muscle. Upon the closing of the uterus, continuous oozing was noted, especially in the bladder flap area, and from the edges of the abdominal incision. No improvement followed the administration of vitamin K. The patient showed signs of shock.

Study of the plasma fibrinogen level with the Fibrindex test showed a marked lowering of fibrinogen, and the plasma clot which formed after addition of thrombin was very small and grossly inadequate. The patient was given an additional 1,500 c.c. of whole blood and 1 Gm. of fibrinogen. The bleeding gradually decreased after the administration of blood and fibrinogen, and the patient was clinically much improved.

On the first postoperative day the erythrocyte count was 3.19 million and hemoglobin 8.95 Gm. The Fibrindex was 5 seconds, control 7 seconds. An additional 500 c.c. of blood was given.

No further bleeding occurred following the initial postoperative hemorrhage. The patient was discharged in good condition on the seventh postoperative day.

Study of the placenta showed all of the cotyledons present. An area of old blood clot located 2.5 cm. from the periphery measured 4 by 3 cm. Microscopic examination of the maternal surface at the site of separation disclosed a laminated, recent blood clot, and strands of fibrin on the decidua basalis and between the decidua and the underlying placental villi.

Comment.—This case is typical of many such cases of abruptio placentae which have been reported[1, 2, 4, 12, 13] with the development of hemorrhagic manifestations becoming greatest at the time of delivery and immediately thereafter. This patient's fibrinogen deficiency was corrected by 1 Gm. of commercial fibrinogen and 2,000 c.c. of whole blood. In view of our present-day knowledge we would have given more fibrinogen and followed her plasma fibrinogen levels more closely.

CASE 3.—Mrs. E. E. S. This 30-year-old para iii, gravida iv, entered the hospital on Jan. 19, 1955, with a diagnosis of missed abortion. Her last normal menstrual period was July 13, 1954. A Friedman test was positive on Aug. 28, 1954. Scanty vaginal bleeding occurred from Nov. 13 to Dec. 4, 1954. A decrease in the size of the uterus, abdomen, and breasts was noted. On admission the uterus was enlarged to the size of an 8 weeks' gestation.

On Jan. 21, 1955, a curettage was performed, with evacuation of a mummified fetus and placental tissue. Bleeding was noted to be somewhat more free than average, but not alarming. The patient, after being transferred to the recovery room, was noted to be bleeding excessively. Shortly afterward the bleeding became very profuse and it was noted that the uterus would periodically fill with blood which was expressed with suprapubic pressure. One cubic centimeter of Pitocin in 1,000 c.c. of 5 per cent glucose in water was given intravenously, with little noticeable effect.

A fibrin assay titer was 1:50, control titer was 1:200. The clot in undiluted blood which formed after the addition of thrombin was grossly inadequate; the erythrocyte count was 4.62 million, hemoglobin 14.1 Gm., and the platelet count 132,000. Five hundred cubic centimeters of whole blood was then given. Bleeding was well controlled with this and constant massage of the fundus. The bleeding decreased progressively. The fibrin assay titer the following morning was 1:100, and two days later 1:200. No further excessive bleeding occurred.

The patient was discharged in good condition on the fourth postoperative day. Study of the placental tissue showed that grossly it had lost its normal spongy consistency and seemed to be firmly coagulated. Microsection showed extensive intervillous fibrin thrombi and an associated extensive degeneration of syncytial tissue (Fig. 2).

Comment.—This case appears to be unique in that only 4 cases of hypofibrinogenemia associated with abortion have been found in the literature, and all 4 have been infected criminal abortions with a fatal outcome.[2, 15] This then appears to be the first recorded case of hypofibrinogenemia with a missed abortion.

As for this patient's therapy, a combination of intravenous Pitocin in glucose solution plus 500 c.c. of blood provided her with proper hemostasis. One must certainly consider Barnes's[16] suggestion of the hemostatic mechanism of myometrial contraction, which may explain part of the hemostasis here.

CASE 4.—Mrs. T. H. E. This 24-year-old para ii, gravida iv, whose estimated date of confinement was Nov. 6, 1955, entered the hospital on Sept. 23, 1955. She was Rh negative and showed increasing Rh antibody titers during this pregnancy. Intrauterine fetal death occurred approximately 8 weeks before admission. The patient had weekly plasma fibrinogen determinations during this interval. These studies were within normal limits until the day before admission when the fibrinogen level was 60 mg. per cent.

The patient was admitted to the hospital for immediate termination of the pregnancy. The plasma fibrinogen on admission was 45 mg. per cent. No hemorrhagic tendencies or bleeding was present. The fundus was at the level of the umbilicus. The cervix was soft, thick, and 1 cm. dilated.

Surgical induction of labor was accomplished by amniotomy 6 hours after admission. The fibrinogen level was determined at this time and was 30 mg. per cent. Six hours later, with mild irregular contractions occurring, intravenous Pitocin in 5 per cent glucose solution was initiated. Four hours later, the cervix was completely dilated and the patient was spontaneously delivered of a mummified female infant. The placenta and membranes were delivered intact immediately after. The fibrinogen was now 10 mg. per cent. An electrophoretic pattern of plasma proteins showed a very minute fibrinogen peak.

No hemorrhagic or bleeding tendencies were detected up to this point; however, immediately following delivery of the placenta, rather profuse bleeding was encountered. One cubic centimeter of Methergine was given intravenously and 1 c.c. of Pitocin intramuscularly. An estimated 500 c.c. of blood was lost during the first 30 minutes following delivery; concurrently 500 c.c. of blood was administered. The bleeding continued, the uterus periodically filling with blood, and contracting with expulsion of gushes of blood and jellylike clots. An estimated 500 to 750 c.c. of blood was lost during the next half hour, and the patient showed signs of early shock. Two grams of fibrinogen was immediately administered. The fibrinogen level was 10 mg. per cent just before and 63 mg. per cent

following administration of fibrinogen. The bleeding subsided to a slow trickle. An additional 1,000 c.c. of blood was then given in addition to a third gram of fibrinogen. The fibrinogen level rose to 85 mg. per cent and the bleeding was now well controlled. Following this, a fourth unit of blood was given. The patient's condition remained good until three hours later when the bleeding suddenly increased. A fourth gram of fibrinogen was given and one hour later the fibrinogen level was 139 mg. per cent.

Fig. 2.

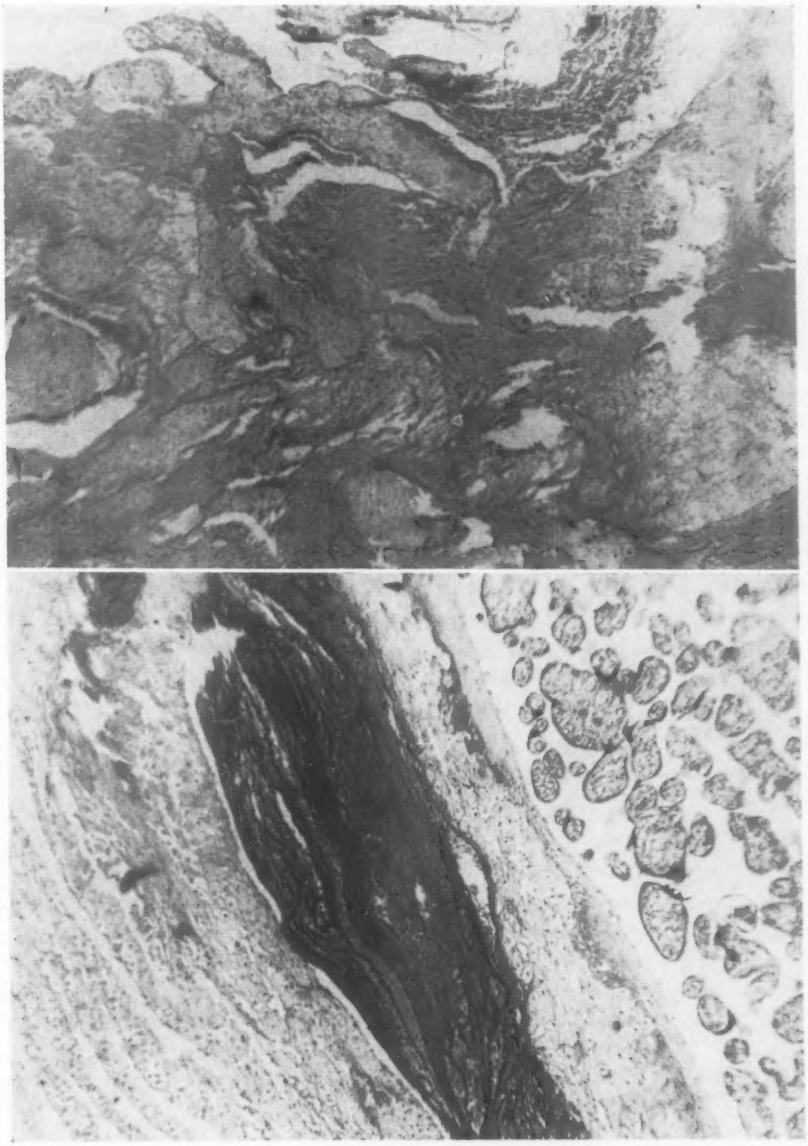


Fig. 3.

Fig. 2.—Histologic appearance of placenta from patient with dead fetus in utero showing more extensive intervillous fibrin thrombosis, with the intervillous spaces almost completely obliterated. (From Ashworth and Stouffer: Am. J. Clin. Path. 26: 1031, 1956.)

Fig. 3.—Histologic appearance of placenta from case of abruptio placentae, showing abundant layer of fibrin at site of placental separation. (From Ashworth and Stouffer: Am. J. Clin. Path. 26: 1031, 1956.)

Her postpartum course from this point was uneventful. A blood count on the first postpartum day showed 3.78 million red blood cells and hemoglobin, 11.3 Gm. The fibrinogen level on the second postpartum day was 185 mg. per cent. The patient was discharged in good condition on the fourth postpartum day.

The placenta grossly did not appear abnormal but had a firm spongy consistency. Histologic study showed a large amount of fibrin as diffuse intervillous thrombosis throughout the placenta (Fig. 3).

Comment.—This patient was followed closely with weekly plasma fibrinogen levels after intrauterine fetal death was diagnosed, in watchful expectation of the development of hypofibrinogenemia. In one week's time the plasma fibrinogen fell from a normal level to 60 mg. per cent and continued to fall sharply prior to any manipulation or intervention. Whether the fall from 30 mg. per cent to 10 mg. per cent which occurred following amniotomy and Pitocin induction was a result of the treatment or mere coincidence cannot be definitely ascertained. We presume that it was coincidence, in view of the sharply falling fibrinogen levels earlier.

Fibrinogen determinations were made frequently in an attempt to correlate the levels with her clinical condition. We believe that this case illustrates what does happen to these patients and we urge earlier prophylactic administration of fibrinogen in the presence of such low levels, rather than waiting for bleeding before administering it.

CASE 5.—Mrs. E. P. S. This 34-year-old para iii, gravida iv, whose estimated date of confinement was May 11, 1956, entered the hospital on Dec. 26, 1955, approximately 4½ months pregnant. Irregular spotting and bleeding had occurred since the last menstrual period. An increase in bleeding occurred just prior to admission to the hospital. Quickening had been noted two weeks before.

Examination on admission showed the fundus to be at the level of the umbilicus. The fetal heart tones were of good quality. Sterile vaginal examination disclosed that the cervix was long, thick, and undilated.

Laboratory studies showed the erythrocyte count to be 3.45 million, hemoglobin 10.5 Gm., leukocyte count 12,000, hematocrit 32 volumes per cent, plasma fibrinogen 122 mg. per cent.

The vaginal bleeding increased progressively. Five hundred cubic centimeters of blood was given and the patient was treated expectantly. The bleeding then showed a progressive decrease during the next two days. Daily fibrinogen levels were 185 and 130 mg. per cent, respectively.

On the third day after admission, the bleeding increased. She was given 2 Gm. of fibrinogen and 500 c.c. of blood. The vaginal bleeding subsided almost completely. The following morning the fibrinogen level was 200 mg. per cent, hemoglobin 10.3 Gm., clotting time 3 minutes, 25 seconds, bleeding time 1 minute, 45 seconds, platelets 215,000.

On the fifth day after admission the vaginal bleeding again increased. The fibrinogen was 150 mg. per cent. Induction of labor was deemed advisable. One cubic centimeter of Pitocin in 1,000 c.c. of 5 per cent glucose in water was started intravenously and the membranes were artificially ruptured. A stillborn male infant was delivered spontaneously 3 hours later. The placenta and membranes were delivered intact. No unusual bleeding was encountered.

The patient had an uneventful postpartum course. On the third postpartum day the fibrinogen was 295 mg. per cent. She was discharged in good condition on the fourth postpartum day.

Gross study of the placenta showed an area of old blood clot along the periphery, measuring 6 by 3 cm. The remainder of the maternal surface presented a granular pale appearance. Microscopic examination at the site of separation showed a thick layer of recent fibrin formation.

Comment.—This case illustrates that fibrinogen depletion can occur with abruptio placentae in early pregnancy, this patient being only 4½ months pregnant. It is believed that this is the earliest that hypofibrinogenemia with abruptio placentae has been described.

The degree of fibrinogen depletion was not great; clinically, however, it appeared to play a role in the bleeding manifestations. Rather prompt control of bleeding occurred following administration of blood and fibrinogen.

CASE 6.—Mrs. F. H. This 22-year-old para i, gravida iv, whose estimated date of confinement was Feb. 19, 1956, was admitted to the hospital on Jan. 10, 1956, with a diagnosis of intrauterine fetal death. The patient was never sure about quickening. No growth of the fundus was noted from 5 months' gestation and a decrease had actually been noted. Roentgenograms 1 week before admission showed evidence of fetal death. The patient was Rh isoimmunized. A plasma fibrinogen level determination done the afternoon before admission was 50 mg. per cent, and the patient was hospitalized for evacuation of the uterus. No unusual bleeding manifestations had been encountered.

Examination on admission showed the fundus to be at the level of the umbilicus. The fetal heart tones were not heard. The cervix was long, thick, and one finger tip dilated.

Laboratory studies showed the erythrocyte count to be 4.1 million; hemoglobin 12.3 Gm.; leukocyte count 10,600; differential normal; platelets 140,000; bleeding time 2 minutes; coagulation time 5 minutes. She was Rh negative, Coombs positive. The plasma fibrinogen was 72 mg. per cent.

Induction of labor was initiated with castor oil and quinine, followed by 1 c.c. of Pitocin in 1,000 c.c. of 5 per cent glucose in water intravenously. The membranes were artificially ruptured 3½ hours later and a moderate amount of bleeding was encountered during amniotomy. One gram of fibrinogen was administered. The bleeding promptly subsided, apparently being due to the manipulation. Three and one-half hours after amniotomy a mummified female infant was delivered spontaneously. The placenta and membranes were delivered intact and profuse bleeding followed. Two grams of fibrinogen was administered during delivery and the bleeding subsided almost immediately thereafter. The total estimated blood loss was 500 c.c. The fibrinogen level one hour after delivery was 238 mg. per cent, Fibrindex 8 seconds, control 8 seconds.

No unusual bleeding was noted thereafter. The patient was discharged in good condition on the fourth postpartum day.

Study of the placenta showed the maternal surface to have a distinct yellow, pale color. It was noted to be very firm and rubbery in consistency. Microscopic examination revealed extensive fibrin deposition throughout the intervillous spaces. Most of the fibrin was of recent appearance and had a fibrillary structure with a few leukocytes and red blood cells intermingled. In other areas the fibrin deposit appeared older and more compact.

Comment.—This patient was admitted to the hospital for evacuation of the uterus as soon as the diagnosis of hypofibrinogenemia was made. Fibrinogen was administered at the onset of bleeding and again at the time of delivery. Delivery occurred suddenly and a moderate blood loss was encountered during the interim from delivery of the placenta until the final administration of fibrinogen.

Comment

Patients with intrauterine retention of a dead fetus are indeed potential candidates for the development of hypofibrinogenemia. Exactly how great this threat may be is still unknown since a sufficient number of cases have not yet been reported. The largest series studied thus far has been that of Pritchard and Ratnoff[5] who found 8 out of 31 women who were undelivered three or more weeks after fetal death occurred. Apparently no one has observed hypofibrinogenemia in cases where fetal death occurred less than 5 weeks before delivery.

In view of our experiences, we believe patients with missed abortion should also be considered candidates for hypofibrinogenemia. Whether this is a common occurrence is not known. It is generally accepted, however, that these patients bleed freely at the time the uterus is being emptied. Perhaps these cases should be considered as belonging to the "dead fetus syndrome."

Once the diagnosis of intrauterine fetal death is made, the patient should be carefully instructed to report bleeding from any site—vagina, mouth, nose, rectum, or subcutaneously. Plasma fibrinogen studies should be done weekly beginning at least 3 weeks after fetal death has occurred. The Fibrindex test is a good screening test, or the more recently developed turbidimetric method of fibrin assay may be used, the results of which are expressed in milligrams per cent. A level below 150 mg. per cent is considered to be below the normal.

We agree with Pritchard and Ratnoff that once the plasma fibrinogen level falls below 150 mg. per cent the uterus should be emptied promptly. The proper procedure should be the method which follows the best obstetrical manner in each individual patient. The majority of patients with hypofibrinogenemia from the dead fetus syndrome will respond to amniotomy with or without dilute intravenous Pitocin. We do not feel as do Vigilante and Behringer[11] that Pitocin is contraindicated in the presence of hypofibrinogenemia.

If induction of labor fails or is considered unfavorable, hysterotomy should then be done unless sepsis is present. Hysterectomy was previously advocated[7] at the time when our first case was encountered. Today it should be done solely on the basis of preventing peritoneal infection in the presence of sepsis.

Fibrinogen should be administered just before the anticipated time of delivery in the absence of any bleeding tendencies. Should any bleeding tendencies occur prior to this, the fibrinogen should be given immediately. Two to four grams should be given intravenously. Those patients whose pregnancies are to be terminated by abdominal or pelvic surgery should be given fibrinogen immediately before operation is begun. Whole blood should be used for immediate blood replacement, and oxytocics used freely. It should be pointed out that commercial fibrinogen may contain the hepatitis virus, and its administration should not be regarded lightly nor should it be haphazardly prescribed. Fortunately, none of our patients who were given fibrinogen subsequently developed hepatitis.

Patients with missed abortion should have a fibrinogen determination done immediately before the anticipated time of emptying the uterus.

Once the uterus is emptied, the plasma fibrinogen recovery is fast. It is usually within or near normal levels 24 hours after removal of the products of conception.

Hypofibrinogenemia associated with abruptio placentae and amniotic fluid embolism has been thoroughly discussed in other reports[1, 2, 3, 6, 12, 13] and does not warrant further discussion here, except to point out that fibrinogen depletion may occur with abruptio placentae in the second trimester as well as the third.

Most authors on the subject of hypofibrinogenemia in pregnancy have referred to and accepted the theories advocated by Page, Fulton, and Glendening[4] and Schneider.[8, 17, 18] This thesis proposes that hypofibrinogenemia results from the excessive liberation of thromboplastin from the placenta and decidua which is then forced into the maternal circulation. The conversion of fibrinogen to fibrin is considered to occur along the blood vessel walls in the maternal circulatory system. This has been shown to occur in the experimental animal following the injection of preparations of placental extracts.[8, 19] The fibrin deposits are then thought by some[4, 13] to be removed by a circulating fibrinolysin.

Dieckmann[20] suggested that in some cases fibrinogen depletion was due to a loss of fibrinogen from hemorrhage, and a mobilization of fibrin at the area of placental separation.

In making a careful study of the placentas in these 6 cases, we were impressed by the amount of fibrin, both fresh and old, which was present in large

quantities on the maternal surfaces and in the intervillous spaces. The amount of fibrin deposited in the placentas in these cases may well account for the fibrinogen depletion which occurs. We have been able to separate from the placenta as much as 28 Gm. of clot that seemed to be composed of apparently pure fibrin in compact form, as judged from histologic studies.

We are of the opinion that hypofibrinogenemia results from a constant process of laying down of fibrin in the intervillous spaces of the placenta in the dead fetus syndrome, and from local deposition of fibrin at the site of placental separation in cases of abruptio placentae, rather than from a process of "hyperthromboplastinemia" in the maternal circulation with resultant deposition of fibrin along blood vessel walls, which then disappears by some questionable fibrinolysin. It is indeed doubtful that a condition of hyperthromboplastinemia is possible since the conversion of fibrinogen to fibrin by active thromboplastin is an immediate reaction. It seems more plausible that the transformation of fibrinogen (from the blood or other body fluids) to fibrin would occur at the site of formation of thromboplastin, that is, in the placenta.

Further to substantiate our theory we are of the opinion that, if the process of defibrination occurs in the maternal circulation rather than in the placenta, embolic phenomena should more often be observed clinically. The clinical symptom complex compatible with significant small-vessel pulmonary embolism has not been observed by us in cases of hypofibrinogenemia, nor reported to our knowledge. In both humans and experimental animals, where fibrinogenopenia has been produced, the lungs have been found to contain only a limited amount of fibrin embolic material. In a review of the photomicrographs of fibrin emboli which have been reported,[8, 18] these have not seemed to us to be adequate in number and extent to produce a state of fibrinogen depletion. It has been suggested[8, 13] that the relatively small amount of fibrin in the lungs resulted from the presence of fibrinolysins that destroy the fibrin thought to have been present. This explanation is difficult to accept in the presence of the concept that small emboli of fibrin are only slowly organized or resolved.

The fibrin deposits in lung capillaries may be better explained as the result of deportation or embolism of fibrin thrombi from the intervillous spaces of the placenta. This may be similar to the well-known process of deportation of giant cells of the chorionic trophoblast to the lungs. These embolic deposits are probably present in slight degrees in many pregnancies without resultant clinical findings of importance. This process may be exaggerated in some conditions (such as hydatidiform mole; probably in instances of dead fetus in utero, abruptio placentae, and amniotic fluid embolism) and possibly to the extent that acute cor pulmonale may occur.[21] We do not agree that the process of fibrin embolism is the cause of depletion of fibrinogen in cases of abruptio placentae and in the dead fetus syndrome. Instead we believe the presence of fibrin emboli in the lungs results from detachment of patches of fibrin from the placenta.

It should be noted that there have been no thorough histologic studies of the placenta described in the recent reports of hypofibrinogenemia in patients with abruptio placentae or a dead fetus in utero. Although we have had an opportunity to study only a few such patients, we have been successful in demonstrating massive formation of fibrin at the placental site in each of them, with evidence that much of the deposit of fibrin was of recent origin. Further studies will be necessary to correlate plasma fibrinogen levels with the amount of fibrin deposited in the placenta.

Summary

1. Six cases of hypofibrinogenemia associated with pregnancy have been reported and discussed, with attention to the deposition of fibrin in the placenta of each. Four of these were of the dead fetus syndrome, one of which was actually a missed abortion, and is thought to be the first such case described. Two cases were associated with abruptio placentae, one occurring at 4½ months' gestation.

2. The diagnosis and management of hypofibrinogenemia in pregnancy are discussed.

3. It is proposed that hypofibrinogenemia results from the deposition of fibrin in the intervillous spaces of the placenta in the dead fetus syndrome, and from local deposition of fibrin at the site of placental separation in cases of abruptio placentae. Histologic studies of the placentas support this thesis.

Grateful acknowledgment is expressed to Drs. Noel R. Bailey and Durwood E. Neal for the data and studies on their patients.

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Discussion

DR. JACK A. PRITCHARD, Dallas, Texas.—It appears that until recently the syndrome of hypofibrinogenemia following prolonged intrauterine retention of a dead fetus was rarely, if ever, encountered in Dallas and according to an ex-colleague it is no longer seen at the institution where I was previously affiliated. It is somewhat comforting to learn that this syndrome is encountered at least occasionally in Fort Worth.

All evidence at this time points to increased utilization or destruction of fibrinogen rather than failure of production as the cause of the hypofibrinogenemia. What becomes of the fibrinogen? Is it converted to fibrin in the intravascular compartment as the result of thromboplastin escaping into the circulation? Is it converted to fibrin within the uterus? Is it destroyed by fibrinogenolysis?

I do not think we can say at this time exactly what happens to the fibrinogen. Dieckmann, who appears to have first demonstrated hypofibrinogenemia in placental separation, thought that most probably the fibrinogen was clotted out in the uterus. Page and Schneider favor intravascular coagulation as the cause of hypofibrinogenemia. Ashworth and Stouffer have observed large deposits of fibrinoid material around the placental cotyledons and suggest that the hypofibrinogenemia results from the deposition of fibrin in this location. Quantitative measurements of the amount of fibrin in the retroplacental clots or around the placental cotyledons certainly are needed. Unfortunately this presents a rather difficult problem in protein chemistry.

In Case 4 it is stated that 8 weeks after intrauterine death the maternal fibrinogen level dropped from normal to 60 mg. per 100 ml. within one week. I am interested in the actual degree of fall per week in this patient. In my experience the rate of decrease has been somewhat less than that suggested by this case. During the past several weeks a patient has been followed at Parkland Memorial Hospital in whom the plasma fibrinogen level fell almost linearly from 505 mg. per 100 ml. to 130 mg. per 100 ml. 8 weeks later.

Next a word about therapy. When fibrinogen is given to correct hypofibrinogenemia I think it is important that we be sure that clinically significant hypofibrinogenemia is present, that is, that the plasma concentration is 125 mg. per 100 ml. or less. Once it is decided to give fibrinogen, a dose of 3 Gm. given at one time when the level is much above 50 mg. per 100 ml. or 4 Gm. if it is below 50 mg. per 100 ml. is probably more efficacious than giving 1 or 2 Gm. at a time.

The use of this agent is not without danger. I have observed homologous serum jaundice in 3 patients who received fibrinogen. Death from homologous serum jaundice has been reported following the administration of only 1 Gm. of fibrinogen. To give fibrinogen to a bleeding patient simply to see if it will stop the bleeding, and then, if it does not, look for other causes of bleeding from the genital tract is to be condemned. This drug should never be used to perform such a therapeutic test.

FIBRINOLYTIC FIBRINOGENOPENIA*

Occurrence in a Case of Abruptio Placentae

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THE serious and often alarming complication of uterine hemorrhage in the parturient, frequently associated with abruptio placentae, has been the subject of a number of recent investigations, which have been thoroughly reviewed.[1-4] Depressed levels of fibrinogen (in contrast to the elevated level of the normal woman at childbirth[5]) are usually found, and have been attributed to various mechanisms: (a) intravascular coagulation associated with the entrance of placental or amniotic thromboplastic material into the maternal circulation; (b) activation of the maternal fibrinolytic system by placental or uterine fibrinolysokinase; or (c) a combination of these two. The demonstration of fibrinolysis has been rare, which may be due to the fleeting presence of fibrinolysin (plasmin) in active form. This present communication presents a single case, in which the fibrinogenopenia and associated coagulation abnormalities can be clearly attributed to the presence of active fibrinolysin in the maternal circulation.

C. J., a Negro para iv, gravida vii, 37 years of age, was first seen at the North Carolina Memorial Hospital on June 17, 1954, when she arrived in labor, having had no prenatal care of any kind. She gave an essentially unrevealing history save for having received a blood transfusion at the time of delivery 4 years previously. On this admission the blood pressure ranged from 200/90 to 160/100. Ocular fundi and urine were normal. One hour after admission she was spontaneously delivered of a living 4 pound 10½ ounce, female infant. She was discharged from the hospital on the fourth postpartum day and failed to keep any return appointments.

She was next seen at 3:30 P.M. on May 30, 1955. The last menstrual period had been in October, 1954, the estimated date of confinement July, 1955. Again she had not seen a physician throughout her pregnancy. At 5:00 A.M. on the day of admission she had first noted vaginal bleeding and stomach cramps. Early in the afternoon she began passing clots and came to the hospital.

Physical examination at this time showed a slightly pale Negro woman who appeared to be in discomfort but not seriously ill. The temperature was 99° F., pulse 96, respirations 22, and blood pressure 170/100. Positive findings were a term-sized rigid, tender, gravid uterus

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with absence of fetal heart sounds or fetal movements and moderately profuse vaginal bleeding. Laboratory findings were: hematocrit 26; hemoglobin 7.0 Gm.; leukocyte count 18,700; polymorphonuclear leukocytes 74; lymphocytes 25; eosinophil 1. There was 2 plus albumin in the urine. The blood type was O, Rh positive.

Intravenous glucose was begun while blood was being grouped and matched. Soft-tissue films of the abdomen revealed a large outline of the uterus with a small fetal skeleton noted in the inferior portion. Above the fetal skeleton, between it and the outline of the fundus, was a large soft-tissue density "which could conceivably represent a tremendous placenta such as occurs in placental apoplexy due to infarction or hemorrhage."

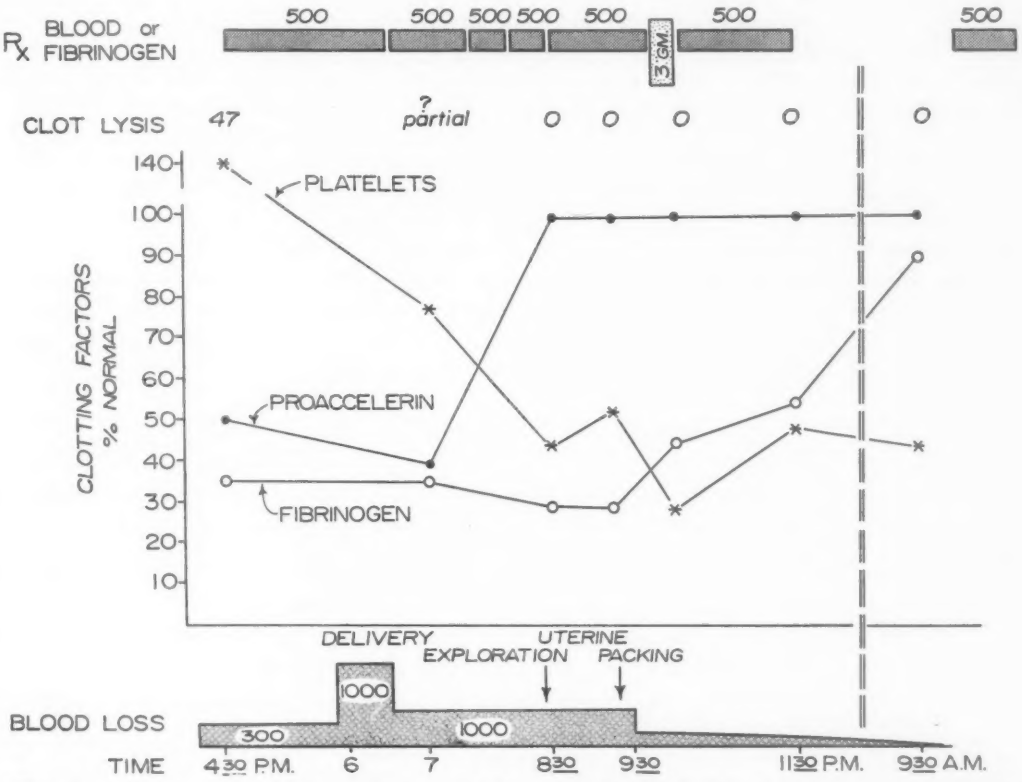

Fig. 1.—Patient C. J. Fibrinogen, proaccelerin, and platelet levels (as per cent of normal) during parturition, complicated by abruptio placentae.

She was transferred to the operating room and at 4:30 P.M. blood was drawn for the special studies which are the subject of this report. The administration of whole blood was begun, and sterile vaginal examination was performed with a double set-up, under nitrous oxide analgesia. Examination disclosed about 200 c.c. of clots in the vagina. The cervix was soft, effaced, 4 cm. dilated, with the membranes bulging. The vertex was presenting in left occipitotransverse position at the spines. No placenta could be felt. The membranes were ruptured artificially and intravenous Pitocin was begun. Labor progressed rapidly and at 6:00 P.M., without anesthesia, the patient was spontaneously delivered of a 2,100 gram stillborn female infant. The placenta and membranes followed immediately with about 1,000 c.c. of blood and old clots. The fundus contracted well. Pitocin and blood were continued. Clotting studies were repeated at 7:00 P.M.

The patient continued to bleed in amounts that were considered excessive although not dramatic, and at 8:00 P.M., under Xylocaine pudendal block supplemented with intermittent nitrous oxide and cyclopropane, exploration of the uterus, cervix, and vagina was carried out, revealing nothing except a few small fragments of placental tissue in the fundus, which

were removed. The fundus remained firm but bleeding continued. At 8:30 P.M. clotting studies were repeated. At 9:15 P.M., since bleeding continued to be excessive, the uterus was packed with gauze and at 9:45 P.M. 3 Gm. of fibrinogen was given intravenously. In retrospect it seems fair to say that bleeding had significantly decreased after 8:30 P.M. and by 10:00 P.M. was within normal limits. At no time was she in clinical shock although one blood pressure reading at 8:45 P.M. was 110/80 with a pulse of 100. Between 4:30 and 7:00 P.M. the patient received 750 c.c. of whole blood and between 7:00 P.M. and 9:45 P.M. she received 1,750 c.c. of whole blood. From 9:45 to 11:30 P.M. she received 500 c.c. and on May 31, during the day, she received 500 c.c. Her total estimated blood loss while under observation was 2,300 c.c. and total replacement 3,500 c.c.

The pack was removed at 6:00 P.M., May 31, without any bleeding. The postpartum course was essentially uneventful and she was afebrile on procaine penicillin. The urinary output, which was 100 c.c. on the day of admission, rose to 2,525, 4,830, and 3,150 on the three following days. The blood urea nitrogen, which was 19 on May 31, rose to 52 on June 2, and dropped back to 21 on June 6. Electrolyte studies showed no alteration. The hematocrit on May 31 was 39.5 and hemoglobin 9.7 Gm. Albuminuria decreased to a faint trace in a voided specimen. The blood pressure, by June 6, had dropped to 130/80 and on June 12, when she was seen at home, it was 120/80. She was discharged in good condition on the seventh postpartum day and again has failed to keep any return appointments.

Methods.—All of the methods employed are either standard procedures or have been previously described.[5, 6] Blood samples were collected in siliconed syringes and transferred immediately to a water bath at 37° C. (clotting time, whole blood fibrinolysis) or to iced containers. Assays were carried out as rapidly as possible to prevent any in vitro effects of fibrinolysin.

TABLE I. BLOOD CLOTTING TESTS

	TIME						
	4:30 P.M.	7:00 P.M.	8:30 P.M.	9:45 P.M.	10:05 P.M.	11:30 P.M.	9:30 A.M.
Clotting time (Glass) (min.)	8	3½	7½	6	7	4½	6½
Clot retraction	–	++++++	+++++	++++	++++	++++	++++
Lysis time	47 min.	>24 hr.	>24 hr.	>24 hr.	>24 hr.	>24 hr.	>24 hr.
Prothrombin consumption %	30	45	50	92	62	73	90
Platelet count × 1,000 per cubic millimeter	395	217	124	146	95	135	121
Prothrombin time*	47	41	86	76	76	88	100
Proaccelerin*	49	40	100+	100+	100+	100+	100+
Prothrombin*	84	63	65	67	58	78	90
Proconvertin	77	62	73	59	56	68	77
Plasma thromboplastin component*	100+	100+	100+	100+	100+	100+	100+
Antihemophilic factor*	100	75	80	100	100	100	100
Fibrinogen*	35	34	30	29	44	54	90

*As % normal.

Laboratory Studies.—These studies are shown in Table I and Fig. 1. The first blood sample, taken some 11½ hours after bleeding had commenced but before transfusion, showed normal clotting, following by the rapid (47 min.) and complete disappearance of the clot. A sample taken some 2½ hours later clotted rapidly, giving a soft rather friable clot which retracted to a very small nubbin but never completely dissolved. Subsequent samples showed no evidence of lysis. Assays of the various coagulation proteins (Table I) showed that on the initial examination only fibrinogen (35 per cent = 116 mg. per cent) and proaccelerin were depressed. The prothrombin time paralled the proaccelerin value. Following whole blood infusions these rose to normal levels. The fibrinogen rose only after the bleeding ceased, in spite of many transfusions and 3 Gm. fibrinogen (Cutter). The other remarkable finding on the initial examination was a low prothrombin consumption (normal = greater

than 90 per cent). As the bleeding and blood replacement continued, a marked fall in platelet count and very slight falls in prothrombin, proconvertin, and antihemophilic factor were observed.

Additional studies of the fibrinolytic enzyme system were not very satisfactory. The initial sample showed lysis of the recalcified plasma clot. Subsequent samples did not. Antilysin titers carried out against a fully active dog serum enzyme showed a slight increase in all the patients specimens as compared to those of 2 normal controls. Streptokinase activation did not differ significantly from that observed in the normal subjects, but this test is subject to error as the fibrin substrate employed (bovine Fraction I) contained plasminogen.

Comment

It was fortunate that the initial specimen in this patient was taken before therapy and at the critical time when whole blood clot lysis could be demonstrated. Thus, it seems justified to relate the accompanying coagulation abnormalities to the presence of active fibrinolysin. In vitro tests have demonstrated the ability of fibrinolysin to destroy fibrinogen and proaccelerin,[7] the two proteins found to be depressed. Lack of intravascular coagulation is evidenced by the normal platelet count and antihemophilic factor levels, as both of these might be expected to be depressed in the presence of even traces of thrombin. Subsequent changes, in particular the fall in platelets, may perhaps be attributed to simple dilution by the 3,000 c.c. of blood which the patient received. Most of this was moderately fresh (less than 48 hours old) but was not taken with any special precautions. After the disappearance of the active fibrinolysin the infused blood may have simply replaced the lost blood. Thus, if release from tissue stores or production of new protein or platelets did not ensue, the levels of clotting factors might be expected to be dependent upon levels in the infused blood. Proaccelerin and fibrinogen reacted in different ways, which the data are insufficient to explain. Fibrinogen showed no rise until bleeding ceased, which was coincident with fibrinogen administration *and* packing of the uterus. The observed rise in plasma fibrinogen would suggest that the infused fibrinogen contained far less than the stated concentration or that it was immediately removed from the circulation.

The cause of the abnormal prothrombin consumption, i.e., the high serum prothrombin level, remains a mystery. Prothrombin consumption is normal in afibrinogenemia,[8] and may be slightly depressed in hypoproaccelerinemia.[6] If it were due to the latter, the consumption would be expected to return to normal as the proaccelerin level rose, which it did not. Perhaps one of the thromboplastic factors, other than platelets, antihemophilic factor, and plasma thromboplastin component, has been depressed.

Summary

A case of abruptio placentae in a 37-year-old multipara has been presented. Initial blood study showed the presence of active fibrinolysin and depressed levels of fibrinogen and proaccelerin. Bleeding was controlled with 3,000 c.c. whole blood, 3 Gm. fibrinogen, and uterine packing.

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A WARM AIR BLOWER* FOR PERINEAL WOUNDS

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PERINEAL incisions, whether obstetrical or surgical, are commonly plagued by certain factors conducive to infection—warmth, moisture, motion, inaccessability, and reinoculation. In an effort to reduce wound complications, surgeons have traditionally employed warm baths because of the effective cleansing action of the solution and the local analgesic effect on the swollen, tender soft tissues. In some of our cases this has seemed to contribute to increased difficulty during the healing process by inducing additional maceration of tissue, and possibly by allowing unsterile water to follow along the sutures into the deeper tissue layers. To minimize these disadvantages, it has been our practice to use wet perineal care only to the extent necessary for cleanliness and prevention of

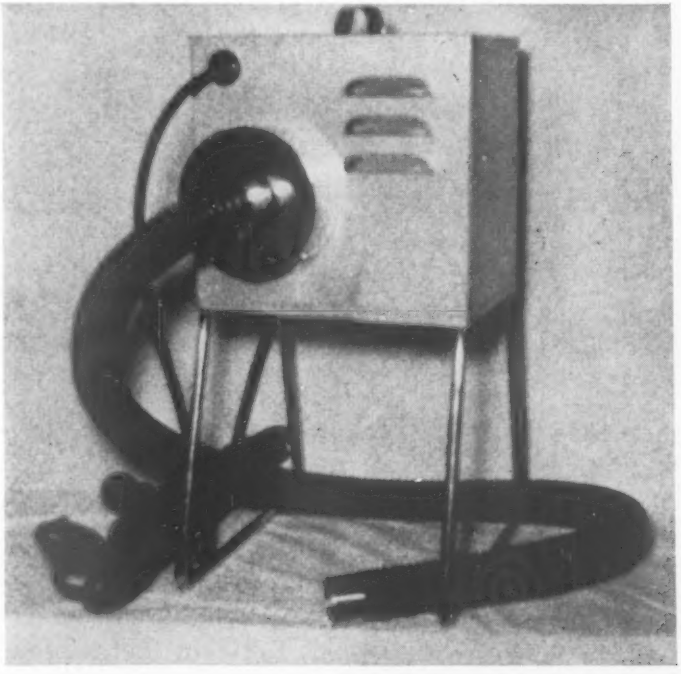

Fig. 1.—Portable perineal blower and drier with thermostatic control and a master switch easily available to the patient.

*The perineal blower and cast drier is manufactured and distributed by Joriman and Williams Manufacturing Company, 1234 Fourth Ave. S.E., Rochester, Minn.

†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

crusting. The major therapeutic attempt has been aimed at keeping the operative site dry. This may be accomplished by simple exposure to air, exposure to lights contained in a protective frame, or by use of a perineal blower.

A perineal blower and drier (Fig. 1) was designed which incorporates several useful factors, as follows: (1) thermostatic control to prevent changes in the degree of heat delivered through the tube, (2) an extension (off-on) master switch to give the patient immediate and ad libitum control of the drier, (3) a delivery tube which is completely sterilizable and long enough to permit placement of the unit itself under the bed during treatment, and (4) an apparatus light enough (12½ pounds) so that it can be moved from room to room with ease.

In practice we use the blower on all patients with perineal wounds, open or closed, at least twice daily for 20 minute periods. The patient assumes a modified lithotomy position with a small soft pillow acting as a bench rest for direction of the delivery tube. No perineal contact is necessary as the stream of warm dry air travels a sufficient distance in sufficient volume to offset any but the most casual aim.

Summary

A safe mechanism for the delivery of thermostatically controlled warm air has been devised. This apparatus has proved useful in the postoperative treatment of perineal wounds.

DISPOSABLE CORD CLAMP THAT ESTABLISHES UNMISTAKABLE IDENTIFICATION OF THE NEWBORN

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THE many methods presently used for identification of the newborn, although varied, are known to all obstetricians. None of them is entirely free from the possibility of error. In order to eliminate error entirely, it is necessary to establish identity before the umbilical cord is severed.

Since the number of hospital deliveries is constantly increasing along with the mounting annual birth rate, all sources of confusion become aggravated. Such factors as two or more deliveries occurring at the same time, or deliveries that take place close to the time of a change in shift of the personnel, or any shortage of personnel contribute to the risk of baby mix-ups. This is a problem that must be faced in almost any institution and its seriousness is so evident that it requires no discussion.

For many years I have visualized a disposable cord clamp to be applied immediately after delivery and before the placenta is expressed or the cord is cut. As the clamp or seal, as it may be called, is applied the initials of the doctor are impressed upon one side of the clamp while those of the mother are impressed on the opposite side. A hemostat may then be placed distal to the clamp and the cord severed. Thus the baby is immediately identified in relation to its mother and the physician.

The proximity of the clamp to the skin margin of the infant will govern the rapidity of dehydration of the cord stump and the time of its separation or dropping off. In cases where exchange transfusion might be indicated, the seal will be applied an inch or more from the skin margin, so that it would be possible to enter the umbilical vein.

Description of Instrument*

The entire equipment may be contained in a plastic box. There are 4 sets of the alphabet properly filed in their own compartments which are so designated as to make it easy for the obstetrician to select his own three initials and snap them into place on one jaw of the instrument while the three initials of the mother are placed on the opposite jaw. In the event of multiple births the figure *2* or *3* (intended for twins or triplets) may be substituted for one of the mother's initials, in order to designate the order of birth of the infants.

In Fig. 1 the cord clamp is shown after being placed in the instrument which may be referred to as the applicator. The construction is such that the clamp stays in place and the device may be handled and the cord sealed with the use of only one hand, leaving the

*This device is patented and manufactured and distributed by Polytronic Research, Inc., 7326 Westmore Rd., Rockville, Md.

other hand free for holding the infant or manipulating the cord. Upon compression of the handles the seal obstructs the circulation in the cord while the identifying initials of the mother and doctor are imprinted as shown.

It has been my custom to assemble the instrument properly previous to delivery and to place it in some antiseptic solution such as alcohol, and then transfer it to the delivery table in anticipation of the actual delivery. The initials to be imprinted are readily visible to the operator on the protruding portions of the lettered strips, so one need not remove the clip in order to see what letters will be imprinted ultimately. Each strip has an embossed letter which comes in contact with the seal or umbilical clamp, as well as a similar letter imprinted on the forward portion of the strip, making it easy to confirm the initials and serving also to simplify filing of the letters in their respective compartments in the plastic instrument case.

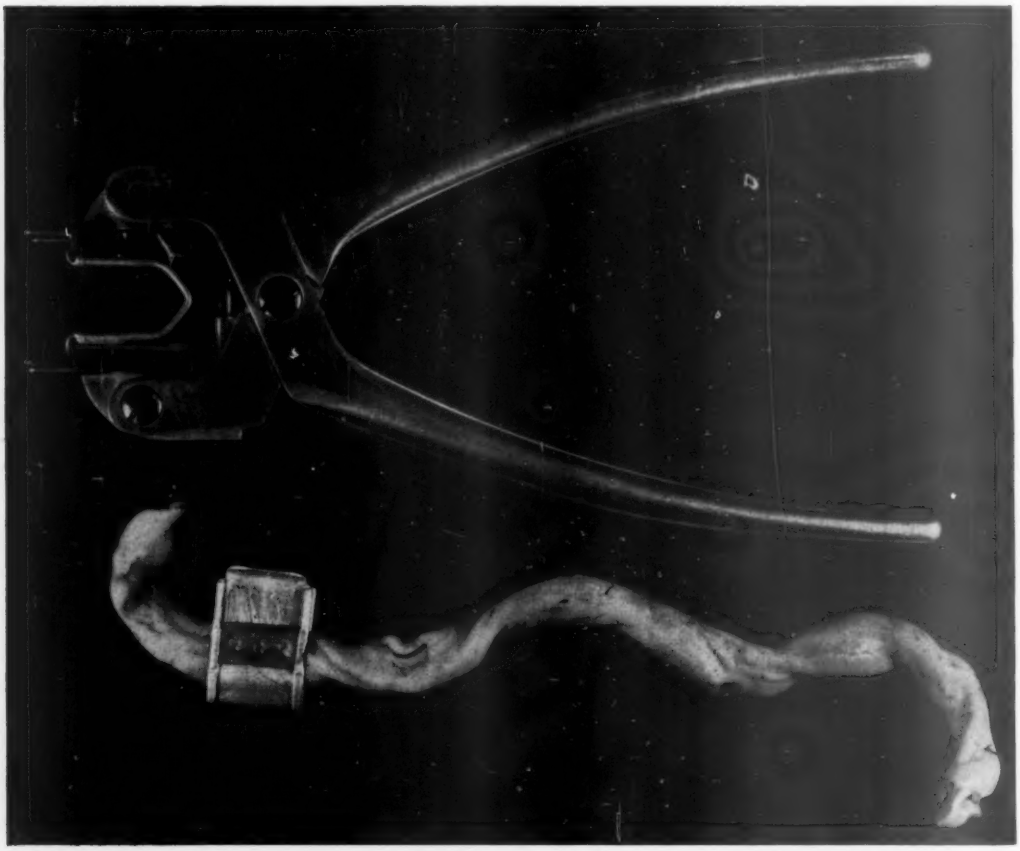

Fig. 1.—One jaw of the instrument is fitted with the three letters denoting the obstetrician's initials, and the other jaw with the mother's initials.

The identifying disposable cord clamp fits snugly into the instrument, enabling application to be performed with the use of only one hand. After the cord is placed in the clamp and the handles of the instrument are firmly closed, the compressed clamp will seal the umbilical vessels and also serve to identify the infant. The procedure is performed before the placenta is expressed, thus eliminating any possible error in identification.

Summary

1. As previously stated, the clamps are not reused and incidentally are inexpensive.

2. The instrument itself will withstand any type of sterilization and will last indefinitely.

3. In most institutions there is always a possibility of deliveries occurring close together, which of course would necessitate having several of the instruments.

4. The doctor assumes all responsibility for establishing the identity of the newborn baby.

5. To insure further security (which hardly appears to be indicated) one may utilize a metal or plastic disk (which may be pink or blue denoting the sex of the infant), with a hole in it for tying to the mother's arm or neck, and with the same identifying initials imprinted upon it.

Washington Medical Building

BANDING THE UMBILICAL CORD

YORK LANCASTER, M.D., PORT LAVACA, TEXAS

(From Calhoun County Memorial Hospital)

THIS article is to demonstrate a simplified method for application of short lengths of tubing to the umbilical cord, with the use of a special "cord bander"* designed for this purpose.

It has been found best to place the rubber band on the instrument while it is dry, put in the "OB pack" ready to use, and all the doctor has to do is go through the simple steps outlined in the illustrations, which are self-explanatory. Be careful not to cut the bands too long, for if the rubber tube is too long, it is inclined to pop off the stretching instrument and fly across the room. Ready-cut bands are available.

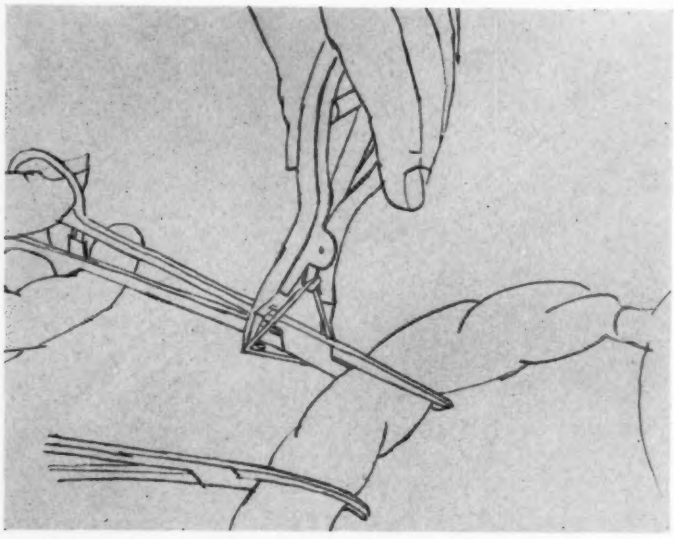

Fig. 1.—Shows the first clamp applied about 15 cm. from the abdomen, and the second clamp reaching through the band stretcher and clamping the cord about 10 cm. from the abdomen.

The advantage of this instrument in applying the rubber band is the two-way stretching of the band, allowing ample room to pull the cord through with ease. The previously published methods using a Kelly hemostat, or an Allis, to stretch the rubber band, stretch it in only one direction, whereas this instrument stretches it in two directions, giving a wider opening and facilitating the placing of the band in the proper position. The rubber bands can be made very simply from waste intravenous tubing of a small diameter which

*Manufactured by Moose Brothers, Port Lavaca, Texas. Distributed by Mills Hospital Supply Co., Chicago, Ill., and W. A. Kyle Company, Houston, Texas.

is washed and cut, by the nurses, in sections ⅛ to 3/16 inch long. It may be that these bands could be made commercially even more cheaply if the nurses' salaries are taken into account.

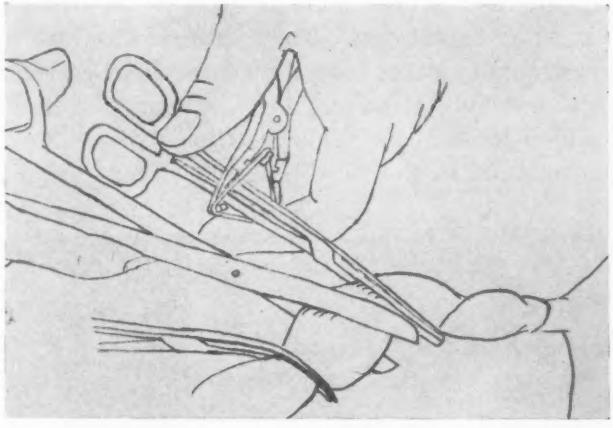

Fig. 2.—Shows the cord being cut close to the second clamp.

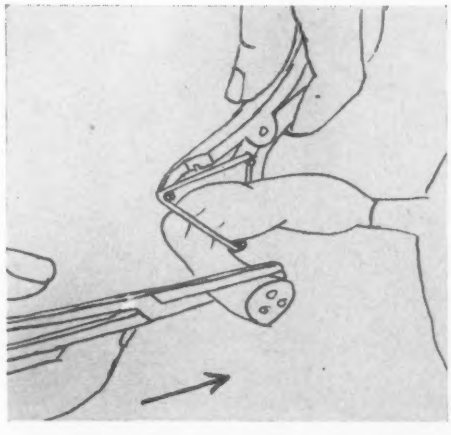

Fig. 3.—Shows the cord pulled through the stretched rubber band by the second clamp, and indicates that a gentle tug in the direction of the arrow will cause the rubber band to slip off the stretching instrument onto the cord. Any excess cord then remaining can be trimmed off, usually leaving about ½ inch of cord distal to the rubber band.

We, and other doctors, have used this method on approximately 900 babies without a single incident of cord bleeding or other complications.

P.O. Box 6
623 North Virginia Street

A NEW FETOSCOPE ATTACHMENT

A. PERELL, M.D., SUMMIT, N. J.

AUSCULTATION of the fetal heart is usually performed with one of the currently popular fetoscopes. These instruments are adequate for this procedure but are generally either too bulky or are fitted with accessories unnecessary for the usual methods of employment. Illustrated in Figs. 1 and 2 is a model of a simplified fetoscope.* This instrument is not designed to improve the physical transmission of the fetal heart tones but does have other advantages.

Fig. 1.

Fig. 2.

Fig. 1.—Fetoscope and diaphragm attachments.
Fig. 2.—Fetoscope held by hand for normal use.

It is small and light and may be carried in a medical satchel or jacket pocket. Frequently the physician requires such a device when examining a patient in her home. In the hospital a personal fetoscope is hygienic and therefore more pleasant to use.

It is convenient to manipulate when examining the obese patient or one on a wide bed. The length of tubing enables the examiner to auscultate both the left and the right quadrants from the same side of the patient. By grasping the hand-head bar, gentle pressure may be exerted to facilitate examining the obese patient.

When bone, as well as air, conduction of sound is desired, the fetoscope may be held against the abdomen with the examiner's forehead on the hand-head bar.

The obstetrical anesthesiologist may listen to the fetal heart tones without leaving the head of the patient when administering an anesthetic.

This fetoscope piece may be interchanged with a diaphragm or may be substituted for the bell in other auscultatory examinations.

*The J. Sklar Manufacturing Co. produced this instrument according to the specifications of the author. This unit is composed of four parts: deep bell, tube fitting, shaft, and hand-head bar.

A MODIFIED RECEPTOR FOR EXTERNAL TOKODYNAMOMETRY*

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SINCE 1947 a multichannel tokodynamometer has been used to measure uterine contractions.[1, 2] The receptors for the tokodynamometer are modified strain gauges called TKD transducers (Fig. 1). Each strain gauge is housed in a metal cylinder which is attached to the abdomen with double-coated Scotch tape.

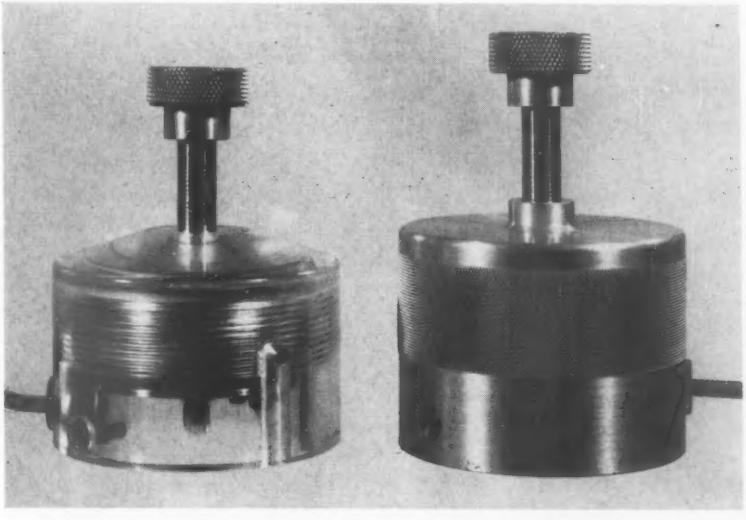

Fig. 1.—Receptors. Plexiglas transducer on the left, TKD transducer on the right.

When the slope of the abdomen is acute, as over the lower uterine segment, the transducer usually will not remain in place long enough to obtain a satisfactory tracing. We used various adhesive substances but failed to solve this problem. It seemed logical that the transducer would remain in position for a longer period if its metal housing were replaced by a material lighter in weight and the unit reduced in height. A Plexiglas housing was produced† which reduced the height of the transducer by 0.95 cm. and the weight by 155 Gm., or 35.2 per cent of the original weight (Fig. 1).

*Aided by National Institutes of Health Grant RG-4703.

†The Plexiglas housing was manufactured by the Royson Engineering Co., 100 North Penn Street, Hatboro, Pa.

The Plexiglas transducer will remain in place over the lower uterine segment for many hours. The advantages of the new transducer include (1) satisfactory performance on any portion of the abdomen, (2) less discomfort to the patient, and (3) reduction of artifacts caused by movement of the patient and/or fetus.

Appreciation is expressed to E. C. Wiegman of Royson Engineering Co., Hatboro, Pennsylvania, for his help and cooperation in the production of the Plexiglas housing.

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1. Reynolds, S. R. M., Heard, O. O., and Bruns, P.: Science **106**: 427, 1947.
2. Reynolds, S. R. M., Harris, J. S., and Kaiser, I. H.: Clinical Measurement of Uterine Forces in Pregnancy and Labor, Springfield, Ill., 1954, Charles C Thomas, Publisher.

PROTOVERATRINE IN TOXEMIA OF PREGNANCY*

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THE role of the Veratrum derivatives in the treatment of toxemia of pregnancy has been a source of controversy since its original use in 1859. Baker[1] was one of the first to use the drug in the treatment of toxemia; but he could not have had much success because he is quoted as saying "*veratrum viride* has seen its day." It again became popular in 1894; but its popularity was short lived and replaced with newer methods by almost everyone. However, the drug has been continuously used with success for the past 50 years at the Cincinnati General Hospital.

Bryant and Fleming[2] in 1940 strongly recommended the use of *Veratrum viride* as an adjunct in the treatment of eclampsia, principally because of its vasodilating properties. This initiated new interest in its application to the treatment of toxemia, and the last few years have produced an increasing number of reports on the use of Veratrum preparations with encouraging results.

Definition

Veratrum viride is found in the roots and rhizome of a plant of the Liliaceae family. It is composed of many different alkaloids, all of which have not been identified. Nevertheless, there are several of the alkaloids that have been isolated and many of these are used now for the therapy of hypertension. Those that are being used have been standardized as to potency, and sterile preparations made available.

Raber[3] summarized well the clinical aspects of *Veratrum viride* when he wrote, "One of the main objections, in the past to the use of Veratrum viride, arose from the fact that it was not standardized, nor the principles isolated; and because of this, the effectiveness of the drug was hampered by the use of crude extracts which were variable in composition and effect, making dosage adjustment difficult and toxic reactions frequent." This objection has been overcome by the preparation of purified, well-assayed extracts of uniform potency, thus permitting standard dosage schedules.

Another objection to its use was its effect on the urinary output. Raber wrote, "There is no doubt that a temporary decrease in urine volume is observed after the first injection of Veratrum, particularly when the blood pressure drops markedly. However, this transitory oliguria is later compensated for by a polyuria which almost always results in an actual urinary increase for the 24-hour period compared to the output for the previous 24 hours."

*Presented in part at the Eighth Annual meeting of the Interurban Obstetrical and Gynecological Society, Buffalo, N. Y., Sept. 22, 1956.

Assali[4] believed that this initial decrease in urine volume is caused by the readjustment of the kidney to the drop in the blood pressure and possibly by an increased secretion of antidiuretic hormone. He stated that there is no evidence to indicate that this transitory oliguria constitutes any danger to the patient's life.

A final objection to the use of Veratrum was the marked frequency of nausea and vomiting and other side reactions. With the use of the newer and more purified forms available today, however, the incidence of toxic reactions has markedly decreased.

The exact pharmacologic action of *Veratrum viride* has not been determined. The drug seems to act by producing arteriolar vasodilatation, with virtually no effect on the venous circulation, thus producing decreased peripheral resistance and a fall in blood pressure with little effect on cardiac output and without the appearance of postural hypotension. The mechanism of the hypotensive action appears to be central in origin with a secondary reflex hypotension. The exact nature or locus of the central action has not been determined. A definite bradycardia is also noted in the patient receiving Veratrum which appears to be due to stimulation of the vagus nerve.

Recent Investigation

Baird and Assali[5] in 1951 reported a series of 38 patients with toxemia, including 3 patients with eclampsia. The Veratrum preparation, Verenteral* was given both intravenously and intramuscularly. They reported that their clinical results were satisfactory with an adequate vasodepressor response in all 38 cases. They felt that Verenteral was of decisive value as an adjunct in the treatment of toxemia.

Alban, Dennis, and Swanson[6] in 1952 reported 10 cases of severe toxemia treated with Veratrone† intravenously. Eight patients in their series had been under treatment by other methods with no response and increase in severity of symptoms. All of their patients treated with Veratrone responded with a prompt fall and stabilization of blood pressure and improvement of symptoms. Side reactions were minimal.

Finnerty and Fuchs[7] in 1953 reported a series of 100 cases of severe preeclampsia and 24 cases of eclampsia. The alternate case technique was used, half of the patients receiving Veratrum preparations, and the others pentobarbital and magnesium sulfate. Their results showed excellent control of blood pressure in patients receiving the Veratrum preparation, while there was virtually no effect on the blood pressure of the other patients. Also there were no cases of oliguria or anuria in the Veratrum group and 50 per cent oliguria and 25 per cent anuria in the second group. There were no maternal deaths and 2 fetal deaths in the Veratrum-treated group as compared to one maternal and 4 fetal deaths in the pentobarbital and magnesium sulfate group. Finnerty and Fuchs concluded that Veratrum therapy afforded a more effective method of management of toxemia than the pentobarbital and magnesium sulfate regime.

A report of the treatment of 205 consecutive cases of eclampsia at the University of Cincinnati General Hospital over a 20 year period with Veratrum preparations shows a corrected maternal mortality figure of 0.5 per cent. This group has long recommended the use of the Veratrum preparation.

In 1956 Krupp[8] and his associates reported a series of 109 patients, 6 of whom had eclampsia, treated with protoveratrine. There was adequate blood

*Irwin, Neisler & Company.
†Parke, Davis & Company.

pressure control in 100 cases, and a failure in only one case. There were no maternal deaths and a 4.3 per cent fetal mortality rate for this series. Krupp concluded that this Veratrum preparation is a potent and effective drug for the release of the vasospasm of toxemia of pregnancy.

The purpose of this paper is to report our experiences while attempting to evaluate a new highly purified preparation of *Veratrum album* made available to us for the treatment of toxemia.

Our series consists of 31 cases of toxemia of pregnancy. The first 9 cases were treated with PVS 295 (Puroverine*) and the remaining 22 cases with protoveratrine A.*

PVS 295 consisted of pure crystallized alkaloids of *Veratrum album,* in ratio of protoveratrine A two-thirds and protoveratrine B one-third. The B fraction is known to be only one-twentieth as effective as the A fraction, and consequently is not felt to contribute greatly to the clinical response.

The second preparation supplied was protoveratrine A, which is simply a more pure preparation of PVS 295, containing the A fraction alone. Therefore our total number of cases (31) is presented in one report because of the similarity of use of and clinical response to these two Veratrum preparations. They are both supplied in parenteral solution and tablets.*

Pharmacology

The pharmacologic study of protoveratrine has been conducted mainly by Krayer[9] and Hoobler[10, 11] in the United States and Rothlin[12] in Switzerland. It has been found to conform to the general pattern of Veratrum compounds as described earlier and as summarized in Table I.

TABLE I. SUMMARY OF PHARMACOLOGIC EFFECTS OF PROTOVERATRINE

Arterial blood pressure	Lowered systolic and diastolic blood pressure	Effects inhibited by epinephrine, norepinephrine, ephedrine
Vessels	Vasodilatation	
Heart	Sinus bradycardia Rarely, arrhythmias	Effects inhibited by atropine
Kidney	Transient oliguria Diminished glomerular filtration Increase of tubular reabsorption	
Side effects	Appear with 130-150 per cent of dose causing hypotension Nausea, vomiting, episgastric or retrosternal pain, diarrhea, paresthesia, excessive bradycardia, arrhythmias	Attenuated by atropine injections

Material and Method

Table II summarizes the total of 31 cases, classified as to the type of toxemia encountered in this series.

TABLE II. CLASSIFICATION OF DISEASE IN 31 TREATED PATIENTS

Severe pre-eclampsia	5
Mild pre-eclampsia	11
Hypertension and superimposed toxemia	7
Eclampsia	4
Postpartum toxemia	4
Total	31

*Sandoz Pharmaceuticals. Parenteral solution, 1 c.c. ampules, 0.1 mg. tablets: PVS 295, 0.25 mg., protoveratrine A, 0.15 mg.

The 31 cases studied included 26 private and 5 ward patients. Of this group, 4 cases of pre-eclampsia were post partum in onset. The remaining 27 cases were diagnosed at varying times during the prenatal period and included 4 cases of eclampsia. The remaining 23 cases included 16 cases of pre-eclampsia and 7 cases of hypertension with superimposed pre-eclampsia.

The patients in this series were routinely treated with protoveratrine, bed rest, salt-free diet, and oral or hypertonic intravenous fluids as indicated. Daily weight, urine, albumin, and fluid intake and output records were kept routinely. Sedation was avoided as much as possible but some patients received occasional small doses of barbiturates, and 2 patients received one to three doses of morphine sulfate. Frequent blood pressure readings were taken on all the patients in this series.

Method of Treatment and Dose Determination

It was noted that individualization of each patient's response to protoveratrine is important. Mild cases of pre-eclampsia were treated usually with oral medication, 1 to 2 tablets every 2 to 4 hours for blood pressure readings above 140/90. The smaller dose is used initially and then increased by ½ or one tablet each 2-4 hours until the desired response is obtained. Patients with severe pre-eclampsia or eclampsia are treated by the method of intravenous titration as set up by Finnerty and Fuchs[7] for other Veratrum preparations in earlier writings. The intravenous route gives the quickest possible response, and is especially valuable in the eclamptic patient.

1. This method consists of diluting 3 ampules of protoveratrine (0.3 mg.) in 30 c.c. of 5 per cent dextrose in water for intravenous use. With one physician recording blood pressure every minute and another administering the medication, give the solution intravenously at the rate of 1 c.c. per minute until the first 20 mm. fall in systolic or 10 mm. reduction in diastolic pressure occurs.

2. Leave the needle in the vein. Do not give additional protoveratrine for there may be a precipitous drop in pressure in the subsequent one or 2 minutes.

3. If after waiting one or 2 minutes no such reduction occurs, proceed at a rate of 1 c.c. per minute, stopping when the blood pressure falls to 140/90 in the previously normotensive patient; or to the prepregnancy level in the case of the hypertensive patient with superimposed pre-eclampsia.

To proceed beyond this point seemed unwise since the maximum response is delayed for about 30 minutes. Blood pressure readings must be continued frequently (every 2 to 3 minutes) for 30 minutes after the titration is completed, to observe any sudden fall in pressure. Both atropine and Levophed or ephedrine should be readily available for intravenous administration in cases of untoward reactions.

The doses necessary for the desired response can be readily calculated from the amount of dilute solution administered (e.g., 20 c.c. = 0.20 mg.). This dose then can be administered undiluted (e.g., 2 ampules) intramuscularly as often as one hour as necessary for a blood pressure of 140/90 or greater. Blood pressure readings should be taken every 15 minutes until the blood pressure and patient's response have been stabilized. Then hourly readings should be routine as well as pressure readings 15 and 30 minutes after any intramuscular dose is given.

As the length of time in treatment increases, patients occasionally become refractory to the initial dose and we have found that increasing the dose by ½ ampule (0.05 mg.) (or ½ tablet) frequently recovers the desired response. One patient who initially responded to 2.5 ampules eventually required 4 ampules (0.4 mg.) for the same response, after a few days of treatment.

When the acute situation has been resolved, that is, when the blood pressure has been stabilized for a safe period, an attempt at oral medication is made, as previously described. None of our patients has required more than 4 ampules (0.4 mg.) intramuscularly or 4 tablets for a satisfactory response.

Results

All but one of our patients responded adequately to the protoveratrine therapy. The one case of failure is reported later in this paper. In general, the severe cases required more vigorous use of the drug under study.

In 19 cases the protoveratrine regime was instituted after delivery (one to 12 hours post partum); in 4 cases because the disease was post partum in onset; in one case of eclampsia because an intravenous magnesium sulfate and barbiturate regime was instituted prior to delivery; and in the remaining 14 cases because active labor had begun before the patient's admission to the hospital, and delivery was imminent. All of these patients were delivered by the vaginal route, following the spontaneous onset of labor in 18 cases and an intravenous Pitocin induction in the one case of eclampsia.

Table III summarizes these 19 cases, showing the patient's age, parity, week of gestation, response to protoveratrine, average daily urine output, and total days of treatment.

Table IV summarizes the remaining 11 cases treated with protoveratrine at varying times during the prenatal period. In this table are also shown the means by which labor was started and the methods of delivery.

The one case which failed to respond to protoveratrine is not included in this table.

The blood pressure response was satisfactory in 30 patients in our series. In the one case of failure, previously mentioned, an initial response to protoveratrine given intravenously was noted; however, prolonged blood pressure control was not achieved.

An average blood pressure reduction of 41.3 mm. Hg systolic and 28.9 mm. Hg diastolic was obtained in these 30 cases with either oral or intravenous protoveratrine. The desired pressure response was obtained within an average of 25.3 minutes when protoveratrine was given intravenously (15 cases) and within an average of 5 hours when given orally (15 cases). Eleven of 12 patients with edema showed a steady decline in amount once treatment had been started. Albumin was noted in 29 of these 30 cases on admission; the degree of albuminuria declined after treatment was started, but all of these patients were reported as having a trace to 3 plus albuminuria at the time of discharge.

Urinary output records were available in 26 cases. The average daily urine output was 2,600 c.c.; one patient with eclampsia averaged 400 c.c. of urine daily before delivery and 3,100 c.c. after delivery.

The average duration of therapy in all cases was 4.3 days, although one patient was given protoveratrine for 15 days. Individual doses were noted to be effective from one hour to as long as 16 hours, with the average effect noted to be 5.4 hours.

Toxic Effects

Toxic effects from protoveratrine were infrequent, not severe, nor did they require discontinuation of the drug at any time. Vomiting was noted in 9 cases, once in 6 cases, several times in 3 cases. Nausea alone was recorded in 2 cases. The nausea and vomiting were noted to be more frequent with the oral preparation and have been reported to be caused by gastric irritation.

Am. J. Obst. & Gynec. February, 1958

TABLE III. PROTOVERATRINE TREATMENT AFTER DELIVERY

PATIENT	AGE	GRAVIDITY	WEEKS OF GESTATION	BLOOD PRESSURE BEFORE THERAPY	ALBUMIN	EDEMA	DOSAGE AND ROUTE OF ADMINISTRATION	BLOOD PRESSURE AFTER THERAPY	LENGTH OF TIME FOR CONTROL	DAILY URINE OUTPUT (C.C.)	DAYS OF THERAPY
1. J. P.	17	i	40	170/120	4+	0	0.27 mg. I.V.	134/90	30 minutes	3,000	4
2. B. P.	24	i	40	150/110	4+	Trace	0.17 mg. I.V.	120/80	20 minutes	2,000	6
3. T. G.	30	ii	34	260/160	1+	0	0.30 mg. I.V.	136/86	30 minutes	1,600	4
4. C. M.	43	xi	40	190/120	Trace	0	0.25 mg. I.V.	160/90	30 minutes	--	3
5. J. W.	21	i	40	190/120	4+	0	0.19 mg. I.V.	144/70	20 minutes	1,600	2
6. B. W.	36	ii	40	190/120	2+	0	0.08 mg. I.V.	124/90	15 minutes	2,000	4
7. R. L.	24	iv	40	170/120	3+	0	0.17 mg. I.V.	138/84	20 minutes	2,200	4
8. J. L.	19	i	40	160/110	4+	0	0.3 mg. p.o.	128/64	3 hours	3,300	4
9. E. S.	29	ii	40	170/100	4+	0	0.6 mg. p.o.	140/90	8 hours	2,200	3
10. D. W.	27	i	40	180/110	4+	2+	0.22 mg. p.o.	130/84	2 hours	2,700	4
11. M. J.	39	i	40	170/100	3+	0	0.37 mg. p.o.	140/86	11 hours	2,100	2
12. E. L.	38	xiv	40	210/120	2+	0	0.60 mg. p.o.	160/90	4 hours	2,100	2
13. F. A.	21	i	40	180/130	0	0	0.27 mg. I.V.	126/86	30 minutes	2,650	4
14. L. K.	39	ii	39	170/96	4+	2+	0.37 mg. p.o.	142/88	2 hours	3,100	7
15. L. J.	30	iii	38	160/108	2+	0	0.30 mg. p.o.	140/80	3 hours	--	1
16. F. W.	34	i	36	150/100	3+	0	0.30 mg. p.o.	128/82	3 hours	2,000	2
17. R. S.	22	iv	39	150/95	3+	0	0.30 mg. p.o.	140/86	3 hours	--	1
18. J. R.	25	i	40	180/120	4+	2+	0.30 mg. p.o.	112/84	9 hours	2,600	6
19. J. M.	22	i	40	160/100	4+	0	0.37 mg. p.o.	132/88	8 hours	2,400	2

TABLE IV. PROTOVERATRINE THERAPY BEFORE DELIVERY

PATIENT	AGE	GRAVIDITY	WEEKS OF GESTATION	BLOOD PRESSURE THERAPY	ALBUMIN	EDEMA	DOSAGE AND ROUTE OF ADMINISTRATION	BLOOD PRESSURE AFTER THERAPY	LENGTH OF TIME FOR CONTROL	DAILY URINE OUTPUT (C.C.)	ONSET OF LABOR	TYPE OF DELIVERY	DAYS OF THERAPY
1. G. L.	28	i	33	180/120	4+	0	0.25 mg. I.V.	138/88	30 minutes	1,700	I.V. Pitocin	Vaginal	15
2. E. C.	25	iii	40	155/90	2+	1+	0.45 mg. p.o.	128/90	2 hours	2,300	Spontaneous	Vaginal	3
3. N. B.	24	i	36	160/120	1+	1+	0.45 mg. p.o.	136/90	4 hours	2,200	Spontaneous* (at term)	Vaginal	6
4. A. M.	16	i	28	245/130	3+	0	0.3 mg. I.V.	160/100	30 minutes	2,500	Bougie in cervix	Vaginal	10
5. H. P.	36	iii	28	164/110	1+	2+	0.37 mg. p.o.	128/84	7 hours	2,500	Spontaneous	Vaginal	2
6. M. A.	22	i	30	180/110	4+	1+	0.20 mg. I.V.	140/90	30 minutes	1,600	Failed induction 3 times	Cesarean section	5
7. R. N.	42	v	40	210/140	2+	±	0.25 mg. I.V.	140/80	30 minutes	1,600	I.M. Pitocin	Vaginal	4
8. B. S.	26	i	33	190/108	4+	1+	0.14 mg. I.V.	140/86	20 minutes	1,600	Bougie in cervix I.V. Pitocin	Vaginal	5
9. C. J.	33	iv	40	160/100	1+	2+	0.37 mg. p.o.	140/90	6 hours	4,000	I.V. Pitocin	Vaginal	6
10. E. W.	27	iii	38	210/160	4+	0	0.2 mg. I.V.	160/130	20 minutes	2,300	I.V. Pitocin	Vaginal	6
11. A. W.	25	i	28	200/120	4+	2+	0.15 mg. I.V.	130/80	15 minutes	1,900	Bougie in cervix	Vaginal	8

*Discharged with complete remission of symptoms—delivered at term.

An antacid usually is sufficient to relieve this condition. In one case, however, when vomiting became a problem, Thorazine was used with good result. Marked bradycardia was noted in 2 cases, but required treatment in only one case. Atropine ($\frac{1}{150}$ grain) is the drug of choice to abolish this effect. Hypotension occurred in one case (blood pressure 90/60) following an intramuscular injection of protoveratrine. This did not recur when the dose was decreased by ½ ampule (0.05 mg.). Shock position and ephedrine or Levophed are indicated to combat this effect if severe or prolonged.

There was one maternal death in this series. This patient was delivered of a stillborn infant before she died. There were 3 other stillbirths, one caused by abruptio placentae which occurred after admission to the hospital. The remaining 2 stillborn infants were severely macerated at the time of delivery. There was one neonatal death of a premature infant that died following operation for a small bowel obstruction.

The maternal mortality in this series was 0.03 per cent and the corrected fetal mortality 0.06 per cent.

Case Reports

In our series of 31 cases there were 4 patients with eclampsia. Two of these cases are briefly described below. A brief summary is also given of the case in which the blood pressure failed to respond to the protoveratrine therapy.

G. K., No. 134421, a 23-year-old white woman, gravida i, in the thirty-third week of gestation, was admitted in a comatose state with a history of 5 convulsions in the previous 2 hours. There were no signs of toxemia during a prenatal checkup 2 weeks earlier. Her usual blood pressure was 100 to 110/70. On admission the blood pressure was 180/110, albumin 4 plus, with minimal edema, and the fundus of the uterus was noted to be 2 fingerbreadths above the umbilicus, with fetal heart tones audible in the right lower quadrant. Immediately, the patient was given morphine, ¼ grain, as was the usual routine in this hospital. Protoveratrine was suggested and given intravenously (0.25 mg. in 25 c.c.) and within 30 minutes the blood pressure fell to 120/180. The patient had one convulsion as the titration was started (blood pressure 180/120). A maintenance dose of 2½ ampules intramuscularly was ordered every 2 hours for a blood pressure of 140/90 or more.

Two hours later the blood pressure was 140/110. Protoveratrine was given and the pressure fell to 140/90. Two hours later the blood pressure was 160/140 and the patient had another convulsion. She was given morphine sulfate, ¼ grain, and 3 ampules of protoveratrine intramuscularly (now ordered every hour for a blood pressure of 140/90). The blood pressure was 130/80 within one hour. Four hours after the last convulsion the patient received the third dose of morphine and 2 hours later was reported as cyanotic with respirations noted at 8 per minute. She was given an ampule of Nalline intravenously and reacted immediately with no blood pressure rise. All sedation was discontinued and the patient subsequently was maintained on protoveratrine plus oral and intravenous fluids. Within 12 hours after admission the patient was alert, oriented, with a blood pressure maintained at 110-140/80-90. The doses of protoveratrine were noted to be effective for periods of 8 to 12 hours. During the 4 days of treatment prior to delivery the patient received hypotonic glucose solutions intravenously. The urine output averaged 400 c.c. per day; the edema increased; the albumin remained 4 plus. On the fifth day she was delivered following an intravenous Pitocin induction. A living 3 pound, 2 ounce infant was delivered and survived. Following delivery diuresis occurred. Intramuscular protoveratrine (0.4 mg.) was continued for 3 days post partum, then oral medication (4 tablets) was used till discharge 9 days after delivery. Some oral doses were noted to be effective for periods up to 16 hours. At the time of discharge the blood pressure was 134-140/70-90, albumin 2 plus, with no edema, Bromsulphalein 6 per cent retention in 45 minutes, and blood urea nitrogen 16 mg. per cent.

9. C. J.	27	iii	38	210/160	4+	0	0.2 mg. I.V.	100/60	20 minutes	1,900	Bougie in cervix Vaginal
10. E. W.	27	iii	28	200/120	4+	2+	0.15 mg. I.V.	130/80	15 minutes	1,900	
11. A. W.	25	i									

*Discharged with complete remission of symptoms—delivered at term.

It was calculated that this patient had received 170 ampules of protoveratrine during the course of treatment, with no ill effects from the drug noted. Figs. 1 and 2 show this patient's response to PVS 295.

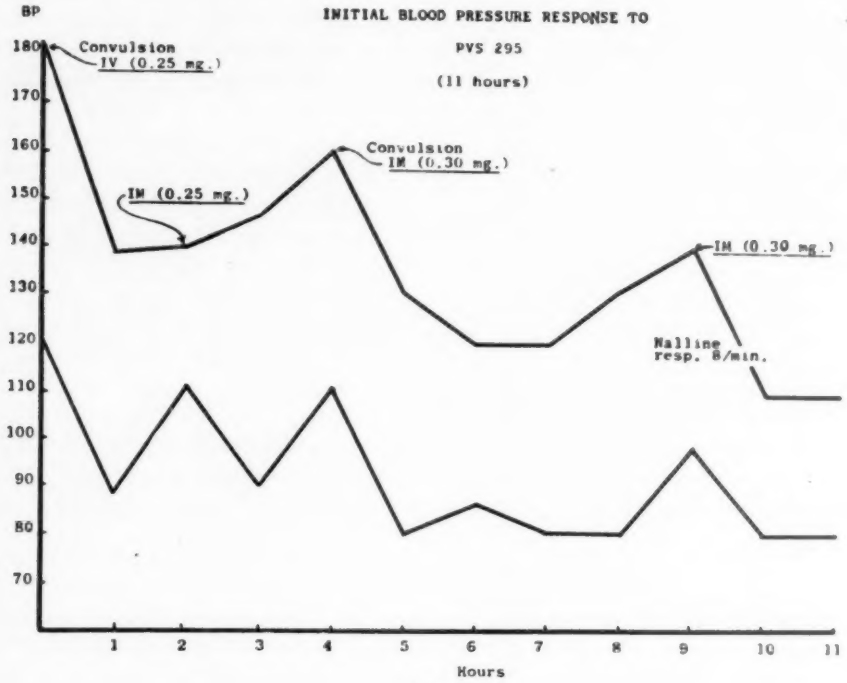

Fig. 1.

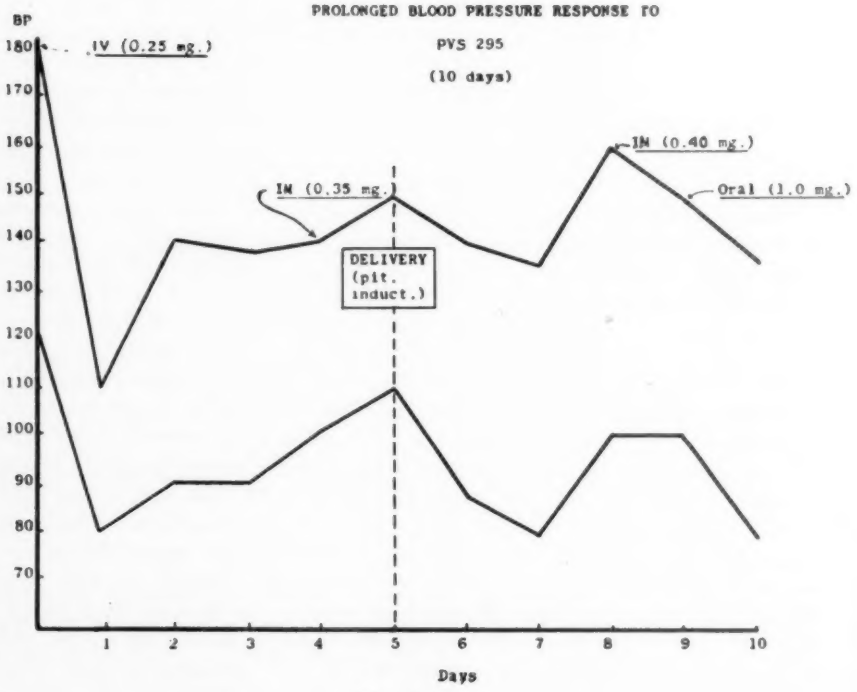

Fig. 2.

J. L., No. 147686, a 19-year-old white woman, gravida i, in the fortieth week of gestation, was admitted to the labor room in coma with a history of 4 convulsions in the previous 2 hours. There were no signs or symptoms of toxemia during a prenatal visit 2 weeks prior to admission, and the blood pressure was 120/85. On admission the blood pressure was 190/130; 4 plus albuminuria and 1 plus pretibial edema were noted. Fetal heart tones were heard in the right upper and left lower quadrants. The patient was given large doses of magnesium sulfate intravenously. The blood pressure fluctuated between 120/80 and 150/100 and the patient continued to have convulsions, until given large doses of barbiturates intravenously. An intravenous Pitocin drip had been started 12 hours after admission but discontinued because of repeated convulsions. Twenty-four hours after admission the blood pressure rose no higher than 150-160/100 and the patient remained in a stuporous state with frequent suctioning of the upper respiratory tract needed. She had been anuric for 6 hours. Another intravenous Pitocin drip was given and the patient was delivered of living twins without difficulty. She remained anuric for another 8 hours even though she had received 3,000 c.c. of 10 per cent glucose solution. The urinary output began to increase; and the blood pressure was noted to be rising from 120/80 immediately post partum to 160/110 16 hours after delivery. She was given protoveratrine (3 tablets) and within 3 hours the blood pressure was stabilized at 128/64. The blood pressure was controlled for 4 days with protoveratrine. The urinary output averaged 3,300 c.c. daily while she was on this therapy. At the time of discharge the patient's blood pressure was noted to be 100-110/70 and a trace of albuminuria persisted.

M. B., No. 144554, a 35-year-old Negro woman, gravida iv, abortions iii, in the fortieth week of gestation, was admitted to the labor room in early first stage of labor. Her blood pressure was 180/108, with 4 plus albuminuria and 1 plus pretibial edema. She complained of headache, blurring vision, and severe epigastric pain. Four hours after admission the blood pressure rose to 220/130 and intravenous protoveratrine was started. After 10 c.c. containing 1 mg. was given, the blood pressure fell to 140/90; this was followed by an almost immediate rise to 210/130. The protoveratrine was continued and an additional 4 mg. (4 ampules in 40 c.c.) given with virtually no effect. The titration was discontinued. The patient continued to complain of severe headache and epigastric pain. Protoveratrine was then given intramuscularly at hourly intervals; the initial dose was 3½ ampules, increased by ½ ampule each hour. Following the last dose of 7 ampules no effect was noted and the drug was discontinued. Two hours after the last dose of protoveratrine was given the pressure began to fall and continued dropping till the patient was noted to be in shock. Fetal heart tones heard on admission were lost at this time. The patient's pressure was maintained with vasopressor agents. The shock was noted to recur when the vasopressor agents were withheld, so a transfusion of 2 units of blood was given. The blood pressure rose to 100/60 and pulse 80. The fundus of the uterus was thought to have risen and a diagnosis of premature separation of the placenta was entertained. Intravenous Pitocin stimulation was given and the patient was delivered of a full-term stillborn infant by low forceps 20 hours after admission and 9 hours after the first episode of shock. At the time of delivery it was noted that premature separation had not occurred. The patient's blood pressure fell again and was not affected by supportive measures. She died 4 hours after delivery, approximately 24 hours after admission. An autopsy showed marked diffuse fatty change in the liver with massive subcapsular hemorrhage in the right lobe and large irregular lacerations in the overlying liver capsule, together with massive hemoperitoneum. The original episode of shock undoubtedly occurred because of this complication of toxemia.

Comment

The foregoing data make obvious the conclusion that protoveratrine is a potent hypotensive agent and when carefully administered will usually control the cardinal manifestations of toxemia of pregnancy without the hazards of heavy sedation or interference with adaptive reflexes.

The foregoing data also demonstrate that protoveratrine does simplify the management of toxemia. It makes unnecessary the use of large doses of barbiturates and narcotics. The patients can be kept conscious, alert, and able to take oral nourishment, fluids, and medication, thereby obviating fluid and electrolyte imbalance and simplifying nursing care. This also simplifies the problem of preparing these patients for early delivery whether by induction of labor or operation.

Because protoveratrine decreases peripheral resistance (vasospasm) it allows increased oxygenation of tissue, thus improving rather than embarrassing the oxygen supply of mother and fetus as would be the case when heavy sedation is used.

Protoveratrine allows control of the blood pressure and pulse rate. Dieckmann[13] stated that an increase in pulse rate over 100 should be regarded as indicating increasing severity of toxemia, and further stated that the mortality rate in eclamptic patients with pulse rates over 120 is 39 per cent. Protoveratrine by its vagal stimulating action causes bradycardia.

The property of Veratrum preparations of lowering blood pressure has never been questioned. The main objection to the use of the crude extracts of the drug was the fear of causing marked hypotension with resultant oliguria and anuria. Protoveratrine, a purified Veratrum preparation, administered as described herein, never produced a drastic fall in blood pressure to collapse levels, nor did it cause oliguria or anuria. Simplicity cannot be claimed in the use of protoveratrine intravenously for the severely pre-eclamptic or eclamptic patient. Constant observation of the patient, frequent blood pressure readings, and prompt treatment when elevations in blood pressure above 140/90 mm. Hg occur are mandatory. In the case of mild pre-eclampsia the availability of purified Veratrum and its effectiveness by the oral or intramuscular route in standard dosage have greatly simplified the management.

Finnerty[7] stated that the main difference between the patients in his "alternate case technique" series was that the Veratrum-treated eclamptic patients were conscious and the barbiturate-treated patients were unconscious. He cited the work of McCall and Taylor[14] on cerebral blood flow and oxygen metabolism in toxemia of pregnancy which showed that barbiturates depress cerebral blood flow and are likely to prolong the coma of eclampsia. This persistence of coma in an eclamptic patient is a very grave sign and is evidenced by a mortality rate of from 34 to 73 per cent in these patients. Finnerty also noted that, in his series of 308 patients, of those treated with pentobarbital there were 6 cases of atelectasis, and in one instance aspiration, which ultimately caused the death of this patient.

Protoveratrine is by no means the final solution or the specific treatment for the toxemias of pregnancy. Neither can we justly attribute the over-all good results in our series of cases solely to the drug, for in most cases spontaneous onset of labor had begun or early induction of labor and cesarean section were employed. However, the value of protoveratrine as an adjunct in the treatment of pre-eclampsia and eclampsia cannot be minimized.

Summary

1. A brief history of the use of Veratrum preparations in the treatment of toxemia of pregnancy is given.

2. A brief description of the source, pharmacologic and clinical effects of Veratrum preparations and protoveratrine is presented.

3. An outline of a safe and effective method of dosage determination for patients treated with protoveratrine is described.

4. A summary of the results in 31 patients with the diagnosis of toxemia of pregnancy and treated with protoveratrine is presented.

5. The case histories of 3 patients in our series are briefly given.

Conclusion

Protoveratrine is an effective and safe drug to be used as an adjunct in the treatment of toxemia of pregnancy until delivery can be effected.

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THE PATHO-MECHANISM OF LATE PREGNANCY TOXEMIA AND OBSTETRICAL HEMORRHAGES

I. Contradiction in the Clinical Pictures of Eclampsia and Placenta Previa Depending Upon the Placental Site

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CLINICAL observation of a certain contrast between eclampsia and placenta previa forms the basis of this presentation. There is no eclampsia in placenta previa cases and, on the other hand, in severe toxemia of late pregnancy low implantation of the placenta is met only exceptionally.

There are only a few notes to be found in the accessible literature dealing with this problem, and they concern the differential diagnosis of bleeding in late pregnancy. The frequent association of toxemia and abruptio placentae was noted by Portes,[16] Dieckmann,[8, 9] Bartholomew,[1, 2] Bland and Rakoff,[7] Irving,[12] and Hertig.[11] In the differential diagnosis the presence of symptoms of toxemia points to abruptio placentae and against placenta previa as the cause of late pregnancy bleeding. Reversing this statement one may infer that the absence of signs of toxemia is characteristic of placenta previa. In fact only Pigeaud,[15] discussing the etiology of toxemia, pointed out the fact that heart decompensation, grave anemia, and placenta previa are practically never complicated by eclampsia.

In order to confirm this observation I asked the most experienced obstetricians with whom I was in touch for their opinion: Czyżewicz, Eastman, Greenhill, Kwater, Lorand, Metler, Roszkowski, Stoeckel, Trapl, Zubrzycki, all corroborated this observation. No one has observed the coexistence of eclampsia and placenta previa. Only Dieckmann had seen one such case, and knew of another one. The association is therefore very rare indeed.

Granzow,[10] referring to Birgus, Decio, and Garcia, stated that placenta previa is rarely accompanied by toxemia. Rauramo[10] did not find any increase in the frequency of toxemia in placenta previa cases, in spite of the opposite statement of Miller[10] that toxic albuminuria appeared in 44.9 per cent of his 49 cases of placenta previa. In an earlier report Young and Miller[18] found albuminuria in 4 of 7 cases of placenta previa. Theobald[17] stated that the marked association of placenta previa with proteinuria has not been confirmed by any other author. He himself observed 107 cases of proved placenta previa during a 5 year period in Bradford, only 5 of which manifested

proteinuria, one of these being a case of toxemic accidental hemorrhage associated with placenta previa. The possibility of abruptio placentae in a low-seated organ was mentioned by Macafee.[13] Mills[14] repeated again that there appears to be some association between placenta previa and pre-eclamptic toxemia.

With the aim of clearing up these contradictory opinions it was decided: (1) to review the material of the First Women's Clinic of the Medical Academy, Gdańsk, for the last 10 years, 1946 to 1955; (2) to ascertain whether eclampsia and placenta previa really do exclude each other; (3) to confirm that the characteristic clinical symptoms of these states are directly opposed to each other; (4) to make possible inferences from these observations in relation to the unsolved problem of the etiology of pre-eclampsia-eclampsia, as well as of the patho-mechanism of obstetrical hemorrhages.

Material and Methods

In 25,000 births there were: 95 cases of placenta previa, the patients' ages ranging from 19 to 44 years, parity from i to xvi; 125 cases of late pregnancy toxemia, the patients' ages ranging from 16 to 45 years, parity from i to vi. There were 57 cases of severe pre-eclampsia, and 68 cases of eclampsia.

All case records of the two series were analyzed similarly as to the characteristic clinical signs—the height of the systolic and diastolic blood pressures, the severity of edema, and the degree of albuminuria. For the strictly measurable values of systolic and diastolic blood pressures, the arithmetic means for the toxemia and for the placenta previa series were obtained, their standard deviations and standard errors, as well as the standard errors of the differences between the means. The significance of the difference was estimated statistically.

For the less measurable clinical symptoms—the severity of edema (severe, mild, and none) and the degree of albuminuria measured in daily urine specimens (severe, over 1 per cent; medium, 1 per cent; mild, 0.5 per cent; trace; none) Pearson's chi-square test was used to evaluate the difference between the placenta previa and toxemia series.

Results

In 95 cases of placenta previa there was no case of accompanying eclampsia. In 68 cases of eclampsia there was no case of placenta previa.

Blood Pressure.—The values of the systolic and diastolic pressures obtained before the beginning of bleeding or therapeutic measures were used. From 95 cases of placenta previa, the values of systolic and diastolic pressures were obtainable in only 77 cases.

The systolic and diastolic blood pressure values in the placenta previa series were usually much lower than the values in the toxemia series (Table I). The standard error of the difference between the means of systolic blood pressures in the placenta previa and in the toxemia series was 2.78, whereas the difference between the means amounted to 57.5, twenty-one times the standard error of the difference.

In the analysis of the diastolic pressure, the standard error of the difference in the two series was 2.03, whereas the difference between the means amounted to 27.5, or 13 times the value of the standard error of the difference. The differences in the systolic as well as in the diastolic blood pressure values

TABLE I. SYSTOLIC AND DIASTOLIC PRESSURES IN SEVERE TOXEMIA AND PLACENTA PREVIA

		DIASTOLIC PRESSURE						SYSTOLIC PRESSURE					
	NO. OF CASES	RANGE	MEDIAN	MODE	MEAN	STANDARD DEVIATION	STANDARD ERROR OF THE DIFFERENCE BETWEEN THE MEANS	RANGE	MEDIAN	MODE	MEAN	STANDARD DEVIATION	STANDARD ERROR OF THE DIFFERENCE BETWEEN THE MEANS
Severe toxemia	125	150-70	110	100	105.8 ± 1.48	16.6 ± 0.98	2.03	230-120	175	160	177.8 ± 2.18	24.3 ± 1.23	2.78
Placenta previa	77	110-60	85	70	78.3 ± 0.44	12.2 ± 1.04		160-90	125	120	120.3 ± 0.55	15.3 ± 1.53	
Difference between the means					27.5						57.5		
Significance					27.5:2.03 = 13						57.5:2.78 = 21		

between the placenta previa and the severe toxemia series were therefore statistically highly significant; i.e., the means differed far more than is likely to have arisen by chance.

Edema and Albuminuria.—The analysis of the other characteristic clinical symptoms, the severity of edema and degree of albuminuria, has shown a similar contradictory behavior in the two series. Whereas a pronounced edema and albuminuria were found almost regularly in the toxemia series, these signs were only exceptionally and in slighter degree found in placenta previa cases (Fig. 1).

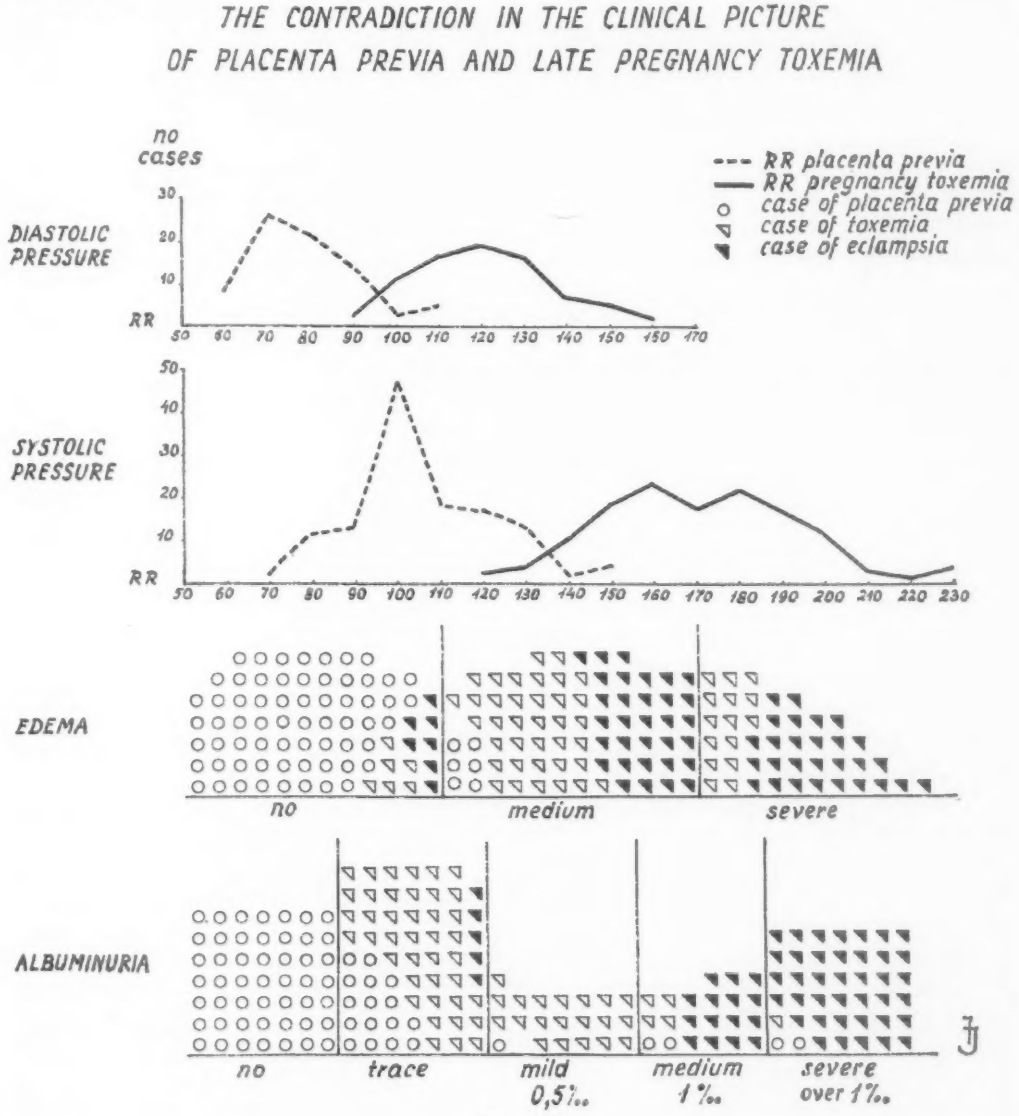

Fig. 1.

Pearson's chi-square test has shown $P>0.01$ when $n = 2$ and $\chi^2 = 121.26$ for edema (Table II); and $P>0.01$ when $n = 4$ and $\chi^2 = 129.41$ for albuminuria in both series of cases (Table III). That means that the severity of edema and the degree of albuminuria in both conditions, placenta previa and severe toxemia, differ to a far greater degree than is likely to have arisen by chance.

TABLE II. EDEMA IN LATE PREGNANCY TOXEMIA AND IN PLACENTA PREVIA

	EDEMA			
	NONE	MEDIUM	SEVERE	TOTAL
Observed number of pregnant women with toxemia	13	69	43	125
Observed number of pregnant women with placenta previa	64	6	-	70
Total number of pregnant women observed	77	75	43	195
Percentage of pregnant women in each edema severity group	39.5%	38.5%	22.0%	100%
Calculation of χ^2 for Edema				
Observed number of pregnant women with toxemia	13	69	43	125
Expected number on hypothesis that toxemia and edema are unrelated	49	48	28	125
Difference observed minus expected	-36	+21	+15	-
(Difference)^2	1,296	441	225	-
(Difference)^2 ÷ expected number	26.44 +	9.18 +	8.03	= 43.65
Observed number of pregnant women with placenta previa	64	6	-	70
Expected number on hypothesis that placenta previa and edema are unrelated	28	27	15	70
Difference observed minus expected	+36	-21	-15	-
(Difference)^2	1,296	441	225	-
(Difference)^2 ÷ expected number	46.28 +	16.33 +	15	= 77.61
				χ^2 = 121.26

n = 2; P in Fisher's tables is much higher than 1:100.

Comment

The analysis of the symptomatology of pregnancy toxemia and placenta previa shows a remarkable contrast (Fig. 1) which cannot be expected to occur by chance; there must be an essential cause for it, correlated presumably with the placental site.

Why are there no conditions for the development of toxemia in placenta previa, whereas, on the contrary, a high placental site probably causes a peculiar predisposition to pre-eclampsia-eclampsia? The simplest explanation lies in the quite different hemodynamic conditions, with the development of a huge uteroplacental circulation on a high abdominal or a low pelvic level. To answer this question observations of the splanchnic vascular system in late pregnancy were carried out during 150 cesarean sections and 14 autopsies of pregnant or puerperal women and compared with similar findings in nonpregnant women. These observations and the respective results are related more thoroughly in further communications.[4, 5, 6] The most important are quoted below, as they are helpful in explaining the different situations with high and low placental site; they are also compared with current views in the literature.

According to most authors the uterus is supplied and drained almost exclusively through the uterine vessels. Only a few take into account the supply of a small fundal part of the uterus through the ovarian vessels, and its

TABLE III. ALBUMINURIA IN LATE PREGNANCY TOXEMIA AND IN PLACENTA PREVIA

	ALBUMINURIA					
	NONE	TRACE	MILD (0.5%)	MEDIUM (1%)	SEVERE (OVER 1%)	TOTAL
Observed number of pregnant women with toxemia	-	46	20	19	40	125
Observed number of pregnant women with placenta previa	49	16	1	2	2	70
Total number of pregnant women observed	49	62	21	21	42	195
Percentage of pregnant women in each albuminuria severity group	25.1%	31.79%	10.76%	10.76%	21.5%	100%
Calculation of χ^2 for Albuminuria						
Observed number of pregnant women with toxemia	-	46	20	19	40	125
Expected number on hypothesis that toxemia and albuminuria are unrelated	32	40	13	13	27	125
Difference observed minus expected	-32	+6	+7	+6	+13	0
(Difference)^2	1,024	36	49	36	169	
(Difference)^2 ÷ expected number	32 +	0.9 +	3.76 +	2.76 +	6.25	= 45.67
Observed number of pregnant women with placenta previa	49	16	1	2	2	70
Expected number on hypothesis that placenta previa and albuminuria are unrelated	17	22	8	8	15	70
Difference observed minus expected	+32	-6	-7	-6	-13	0
(Difference)^2	1,024	36	49	36	169	
(Difference)^2 ÷ expected number	60.29 +	1.63 +	6.12 +	4.5 +	11.20	= 83.74
						χ^2 = 129.41

n = 4; P in Fisher's tables is much higher than 1:100.

high drainage uphill through the long and narrow ovarian veins to the middle abdominal zone.[9a] There are herewith two potential uterine circulations: the caudal, lower one, carrying the bulk of blood through the pair of right and left uterine vessels on the pelvic circulation level, and the cranial, higher one, less significant, connecting the uterus from deep within the pelvis with the renal circulation level through a pair of right and left ovarian vessels.

The uterine circulation does not show that degree of constancy which has commonly been supposed. From the potential circulations the blood may be driven either almost exclusively through the lower routes (e.g., in nonpregnancy states or in placenta previa), or through the higher pathways (late first pregnancy and labor), or to a varying degree through both (multiparas). Fundamental changes occur in the course of the blood through the potential circulations and, in fact, the direction of drainage of the uteroplacental circulation is different and individual in every pregnancy, depending on several conditions: (1) the height of the placental implantation, which is the center of the uteroplacental circulation, determining its development on a low pelvic or high abdominal level; (2) the resistance met by the blood current in different

possible directions, dependent on the breadth and length of the respective draining system and the hydrostatic pressure which has to be overcome; (3) the flexibility or firmness of the vascular wall, determining the capacity of the venous draining vasculature to accommodate the increased blood quantities, to form blood lakes and resorvoirs; (4) the possibility of developing vascular communications and anastomoses for further extension of blood drainage. Of great importance for the pathomechanical influence of the blood redistribution is (5) the state of filling up of the intravascular compartment dependent on the fluid balance of the pregnant organism. (6) the rate of flow of blood driven per time unit through the uterine circulation.

In primiparas the usual normal or fundal site of the placenta favors the development of the uteroplacental circulation on a high abdominal level. With the huge increase of the pregnant uterus and its displacement from deep within the pelvis, the ovarian vessels form very nearly the sole visceral drainage route from that high elevated part of the organ, protruding freely into the abdominal cavity. The resulting shortening and relaxation of the ovarian plexuses enables their broadening and hypertrophy, under the influence of placental hormones, and the carriage of the blood volume increased almost 70 times in comparison with that of the nonpregnant state.[11a] Otherwise the uterine vessels, which run straight downhill along the lateral margins of the uterus, become enlongated and narrowed during the first pregnancy, when they meet the difficult task of tracing the uterine body on its way high up. The great resistance met in connection with these changes by the blood current in the downhill direction (in its normal course through the uterine vessels) is visibly increased during labor with the additional obstruction formed by the engaged head.

According to Poiseuille's law, $Q = \frac{P\ R^4\ t}{8\ L\ n}$, where Q is the volume of fluid flowing through a tube in time t, P is the fall of pressure in the flow direction over length L, R is the radius of the tube, and n the coefficient of viscosity, the bulk of the uteroplacental blood is driven in the direction of the least resistance—through the large ovarian veins, and not through the narrowed and elongated uterine plexuses. The passage of huge uteroplacental blood masses predominantly through the high drainage routes to the renal circulation level, and further on through the splanchnic anastomoses, ovarioenteral and renoportal communications to the liver, and/or through segmental communications, the vertebral venous system to the great sinuses of the central nervous system, must be followed by an increased blood volume and pressure—venous hypervolemia in those regions: the kidneys, liver, and brain. The new redistribution of blood masses to the visceral venous system with an imposed increased work load releases severe hemodynamic disturbances in those vital and highly differentiated visceral organs peculiarly sensitive to hypoxia. The hemodynamic disturbances of vital visceral organs resulting from a predominant high drainage of the uteroplacental circulation, showing an enormous increase in late pregnancy, may account for all the functional and anatomopathological changes in vital organs, and for the resulting clinical symptoms and signs characteristic of pre-eclampsia-eclampsia.[5, 6]

In placenta previa, on the contrary, the development of the huge uteroplacental circulation on a low, pelvic level directs the course of blood through the lower, caudal circulation. With the broad implantation of the pregnant uterus in the neighboring parametrial structures, there are plenty of anastomoses and parietal drainage possibilities in all directions through muscular,

skeletal, segmental communications and external and deep subcutaneous networks. The backflow of blood predominantly through parietal pathways is secured without disturbing the hemodynamics of vital vesceral organs.

In multiparas the drainage routes from the pregnant uterus show usually an intermediate course between the conditions found in primiparas and those in placenta previa. In contrast to young girls and nulliparas in whom the uterine vessels have a straight course, in parous women they are markedly tortuous.[9a] It is the effect of their lengthening during the first pregnancy which permits the easy unfolding, development, and hypertrophy of the uterine vessels, without elongation and narrowing, in the coming pregnancies. The drainage downhill is more easy, especially with the usually lower placental site in multiparas. Finally, the more flexible vascular and muscular tonus allows hydrostatic factors to prevail, with the gravitation of blood to the lower drainage routes, even if the placental site is exceptionally high. The diversion of a large part of the uteroplacental blood downhill to the pelvic circulation level lessens the stress on renal and visceral hemodynamics characteristic of primiparas. Otherwise, in connection with a marked divergence in late pregnancy between a free blood supply and a hampered backflow from the uteroplacental circulation, hemodynamic disturbances on the low, pelvic level may be released, with grave, hemorrhagic consequences.

The enormous development of the uteroplacental circulation in late pregnancy and its function as arteriovenous shunt[11a] increase the work load on the highroads of backflow just in a period when the main draining thoroughfare, the inferior vena cava, is overfllled and obstructed by the stress of the pregnant womb. Taking into consideration the difficulties in further propulsion of the blood mass, the pelvic venous system must undergo, as it does especially in multiparas, extraordinary adaptative changes, to accommodate the increasing blood volume. The magnitude of the alterations in the work load imposed on pelvic veins in that situation may be paralleled only by the stress in the visceral venous system in cases of a predominant high drainage of the circulation in primiparas. Otherwise it is unparalleled in human physiology. The unique ability of pelvic veins to dilate, permitted by the absence of the fascial sheath, probably serves to neutralize greater pressure changes. The tension of individual vein walls calculated by Laplace's law nonetheless increased approximately 2.86 times from nonpregnancy to pregnancy.[11a] The expansive tension within the blood resorvoir of the pelvic vascular system may steadily increase with the congestion and venous engorgement. The effective pressure of the enclosed blood mass upon the placental surface during pregnancy or upon the placental site in and after labor (third and fourth stages), may be a decisive factor in the pathological mechanism of obstetrical hemorrhages.[4, 5]

The classical division of postpartum hemorrhages into (1) traumatic, and (2) atonic, is incomplete, not only because it omits (3) the important group of hemorrhages from coagulation defects (*Ungerinnbarkeitsblutungen*[4]). More essential is the omission of (4) the hypervolemia congestion factor, a decisive one in all obstetrical hemorrhages. It is the dynamic force of the expansive tension gathered in congested blood masses, engorged within the pelvic venous system.

There is only one hint in the relevant literature mentioning the possible connection between the placental site and the etiology of eclampsia: Dieckmann[9] wrote on page 365 of his book, *The Toxemias of Pregnancy:* "The possibility of placental and uterine ischemia is an attractive one because one can postulate that the placenta in the pregnancy in which pre-eclampsia-eclampsia occurred was attached to the uterus in an area in which the blood supply could not be maintained at the optimal blood flow under normal conditions. This

might be in one horn of the uterus or it might be either on the anterior or posterior wall just above the cervix. In either of these sites the blood flow would probably not be as great as if the placenta were implanted close to one of the uterine arteries." According to our observations it is not the problem of blood supply conditions but rather of the direction of blood drainage from the uteroplacental circulation and the resulting hemodynamic disturbances.

The observations of Young and Miller,[18] Miller[10] Macafee,[13] and Mills[14] of a coexistence of placenta previa with certain signs of pre-eclampsia might contradict our own conception. It can be easily explained, however, by the large size of the placenta so often noticed when it is low seated. A very large placenta previa might reach even the fundal region and then discharge a tremendous part of its great blood flow to the high circulation level of the kidneys and liver, producing some signs of pre-eclampsia, or even, in a very rare case, eclampsia.

The contradiction between the two clinical pictures of eclampsia on the one hand, and placenta previa on the other, might be explained by the quite different drainage conditions of the uteroplacental circulation, either up- or downhill in late pregnancy. In fact, pure forms with an exclusive discharge in one direction or the other are not often met in practice, the course usually going to a varying degree in both directions. The strong current of the uteroplacental circulation, dangerous in its "one-course drainage," wastes its vigor, scattered into several small streams. Nonetheless, it may sometimes cause hemodynamic disturbances with toxemia and hemorrhage both in the high and in the low region, when the placenta is large, the rate flow per time unit enormously increased, and the intravascular compartment of fluids overfilled, e.g., in abruptio placentae, multiple pregnancy, or hydatiform mole. All these states, prone to toxemia and hemorrhage, form a link between the contradictory clinical pictures of eclampsia and placenta previa.

Conclusions

1. There is a marked contrast between the clinical pictures of eclampsia and placenta previa.

2. They do, in a certain measure, exclude each other: in 25,000 births with 95 cases of placenta previa and 68 cases of eclampsia there was not a single case of coexistence of these two states.

3. The systolic and diastolic blood pressures are usually distinctly lower in the placenta previa series than the respective values in the toxemia series.

4. A similar contradiction in the other characteristic clinical signs was shown: whereas no edema and no albuminuria were typical of placenta previa, severe proteinuria and marked edema were pathognomonic for toxemia.

5. The difference in the values of the clinical signs of eclampsia and placenta previa is statistically highly significant, far more than is likely to have arisen by chance.

6. The absence of signs of toxemia in bleeding of late pregnancy indicates placenta previa, whereas the presence of these signs is diagnostic of abruptio placentae.

7. A working hypothesis is drawn that toxemia of late pregnancy and obstetrical hemorrhages are expressions of the same disturbance in a different pattern, namely, hemodynamic disturbances caused by the development of a huge uteroplacental circulation in late pregnancy and showing a quite different effect depending upon whether the direction of drainage is high or low.

With a predominantly high drainage through the ovarian veins and further visceral communications, hemodynamic disturbances in vital visceral organs result, which may account for all functional and pathological changes characteristic of pre-eclampsia-eclampsia, and of the resulting clinical signs.

With a predominantly low drainage of the uteroplacental circulation through the uterine plexuses, grave hemodynamic disturbances on the low pelvic level may result from a marked divergence between a free blood supply and a hampered backflow. The dynamic tension and effective pressure of the congested blood mass upon the placental surface during pregnancy, or upon the placental site in labor, may be the decisive factor in the patho-mechanism of obstetrical hemorrhages.

Summary

In 25,000 births, with 95 cases of placenta previa and 68 cases of eclampsia, there was not a single case of coexistence of these two states. A comparison of the most outstanding clinical signs has shown a certain contradiction in the clinical pictures: Whereas low blood pressure, no proteinuria, and no edema were characteristic of placenta previa, high blood pressure, severe proteinuria, and marked edema were pathognomonic of toxemia. A statistical analysis has shown that this contradiction may not have arisen by chance and that there must be an essential cause for it, correlated presumably with the placental site.

A working hypothesis is postulated of the pathological mechanism late pregnancy toxemia and of obstetrical hemorrhages as a result of hemodynamic disturbances connected with the development and drainage of the uteroplacental circulation in late pregnancy.

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PREFRONTAL LOBOTOMY AND SEVERE PRE-ECLAMPSIA*

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PREFRONTAL lobotomy is a surgical procedure wherein the frontal lobes are separated from the remainder of the brain. This operation has been frequently performed for the past 22 years for various types of serious mental disorders which were not amenable to other forms of therapy. In most instances, following lobotomy, the individual becomes peaceful, cooperative, carefree, no longer hostile or suspicious, and more tolerant to pain. Generally the patient behaves in a good-natured manner even in the midst of unpleasant circumstances.

No case report could be found in which pregnancy occurred in an individual who had had a prefrontal lobotomy. The clinical course and general behavior of a patient with severe pre-eclampsia several years after lobotomy is therefore presented.

Case Report

Mrs. H. G. (Hospital No. 272807) a 37-year-old white woman, para ii, gravida iii, with a pregnancy at term, was seen for the first time in consultation in the labor rooms of the Mount Sinai Hospital on April 6, 1956, because of toxemia. The expected date of confinement was April 1, 1956. Her antenatal care had been inadequate because she failed to follow her family physician's instructions. She was examined only three times during a 7 month period.

The abdominal cramps which made her come to the hospital stopped soon after admission to the labor rooms. No significant facts were elicited from her menstrual or family history. The previous obstetric history disclosed 2 normal pregnancies and deliveries which occurred in 1942 and 1945.

Generally her health had been satisfactory except for schizophrenia, for which she was hospitalized in 1938, 1951, and 1952. A prefrontal lobotomy was performed Jan. 20, 1952, and resulted in a great improvement in her psychosis. During the past 4 years she had been self-sufficient and had been able to carry on her usual household tasks without any difficulties.

Physical examination showed a moderately obese 37-year-old white woman exhibiting a state of well-being. Her temperature was normal. The pulse rate was 92 per minute and the blood pressure reading was 158 systolic and 112 diastolic. The head and neck were normal except for puffiness of the eyelids and two small scars in the frontal region of the scalp. The heart and lungs were normal. There was 1 plus pitting edema of the lower extremities. The abdomen revealed a pregnancy with a McDonald measurement of 32 cm. The position of the fetus was left occipitotransverse and the heart tones were of good quality and 140 per minute. Rectal examination disclosed a long, closed, uneffaced cervix. The presenting part was high but could be impressed to a minus 2 station. It was estimated that the infant weighed between 4 and 5 pounds. The urine showed 1 plus albumin and was negative for sugar and acetone.

*Presented at a meeting of the Chicago Gynecological Society, May 17, 1957.

The immediate management consisted of absolute bed rest, blood pressure reading every 4 hours, daily weight determination, Sodium Amytal, 3¾ grains intravenously, 4 c.c. of 50 per cent magnesium sulfate intramuscularly at once and twice daily thereafter, salt-free diet, measurement of intake and output of fluid, daily examination of 24 hour urinary output, phenobarbital, 1 grain four times a day, with Seconal, 1½ grain as needed, for sleep. A complete blood count, blood urea nitrogen and blood uric acid determinations, and x-ray studies to rule out abnormalities of the fetal skeleton were also ordered.

The day following admission, the patient's condition appeared to be improved. The blood pressure dropped to 110 systolic and 70 diastolic, the measured output of urine was 1,470 c.c. and it contained 0.23 Gm. of protein. The blood urea nitrogen was 10 mg. and the uric acid 5.4 mg. per 100 c.c. of serum. X-ray studies showed a small baby with normal skeletal structures. The distal femoral epiphyses were visualized.

For the next 3 days the patient's condition remained satisfactory. Medical induction of labor was planned as soon as it could be accomplished successfully. However, late in the evening of April 10, there was a sudden elevation of the blood pressure to 170 systolic and 110 diastolic. The urinary output of the previous 12 hours was approximated to be only 300 c.c. and a 2 plus to 3 plus albuminuria was present. Since the cervix was found to be closed, long, and uneffaced, it was decided that termination of pregnancy by cesarean section would serve best the interests of the mother and baby. Accordingly, a low cervical cesarean section was performed on April 10, 1956, 4 days after admission to the hospital. Local anesthesia, 1 per cent Xylocaine, was employed. A Pomeroy tubal ligation was done prior to closure of the abdomen.

The baby weighed 4 pounds, 4 ounces (1,928 grams), and cried vigorously.

The patient became critically ill soon after delivery. Cyanosis, tachycardia, hypertension, oliguria, albuminuria, hemoconcentration, and severe paralytic ileus prevailed for approximately 6 days after operation. The management consisted of the administration of intranasal oxygen, antibiotics, antihypertensive drugs, sedatives, rapid digitalization, Wangensteen suction, rectal tube with frequent irrigation of the lower bowel, a Foley catheter, and adequate amounts of glucose and/or saline and potassium chloride intravenously as indicated. Numerous laboratory determinations were frequently made to aid in therapy.

In contrast, the general behavior and tranquillity of the patient did not at all reflect her critical state of health. It was most remarkable to watch her exhibit a sense of well-being while rubber tubing was draining almost every orifice of her body, and with almost constant immobilization of at least part of one extremity for the intravenous fluids.

She offered no resistance to anything that was done for her. In fact she frequently smiled and even joked during intravenous puncture or while a catheter was being inserted into the upper or lower orifice. She repeatedly requested a cigarette or asked for something to eat but at no time insisted on having it. She radiated optimism constantly. If she felt or had any insight regarding the gravity of her condition, it was not apparent to any one who visited her.

Definite improvement became apparent 7 days after delivery. The patient left the hospital on the thirteenth day after operation. The infant remained in the premature station for 22 days and left the hospital in good health weighing 5½ pounds. Re-examination one year after delivery showed that the patient was in good health without any evidence of cardiac, renal, or vascular disease.

Comment

The patient's personality and general behavior caused by the lobotomy was a factor in her failure to obtain adequate prenatal care which contributed to the development of the toxemia. Her constant euphoria and display of a sense of well-being frequently masked the critically grave state of her health. In the presence of severe hypertension, cyanosis, tachycardia, dyspnea, marked abdominal distention, rubber tubing in both nasal passages, a Foley catheter in the bladder, a rectal tube, and with almost constant intravenous fluids, she had

almost no complaints. When awake or aroused, her attitude was always optimistic and cheerful. Her only interest was smoking, eating, and going home to her family. Since she had such a high threshold of pain and discomfort, her management was made very easy. She accepted all treatment without the slightest objection.

If other women with prefrontal lobotomy behave in a similar manner, then their care during pregnancy requires special attention. Because of lack of interest these women may fail to keep their antenatal appointments. The husband or other members of the family must be impressed with the importance of prenatal care so as to avoid the omission of regular periodic examination by the attending physician. To avoid a precipitate delivery, they should be urged to report to the hospital soon after labor begins. Careful observation during labor and the postpartum period is advisable since the patient may fail to report excessive bleeding or any other abnormalities.

Summary and Conclusions

1. A case of severe pre-eclampsia in association with prefrontal lobotomy is presented.

2. Even though the patient was critically ill she continued to exhibit a sense of well-being.

3. The state of euphoria, the carefree attitude, the high threshold of pain, and the excellent cooperation of the patient were of considerable aid in her management and perhaps in her ultimate recovery.

4. It is suggested that because of their carefree attitude, individuals who have had prefrontal lobotomy be urged to carry out all instructions meticulously and to attend regularly prenatal visits.

5. Cooperation of the husband or other responsible member of the family must be enlisted to accomplish the desired result. Furthermore, because of a high threshold of pain, special care may be necessary to prevent precipitate delivery as well as to prevent other complications of which the patient may fail to complain.

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Editorial

APPOINTMENT OF NEW EDITORS

On the cover and editorial page of the January, 1958, issue of the JOURNAL appeared the names of the new Editors, appointed following the death of Dr. William J. Dieckmann.

In the future there will be three Editors, Dr. Howard C. Taylor, Jr., of New York, Dr. John I. Brewer of Chicago, and Dr. Allan C. Barnes of Cleveland. Dr. Louis M. Hellman will remain as Editor of Book Reviews and Abstracts.

The selection of the two new Editors was made on the recommendation of the Advisory Editorial Committee at its fall meeting. Since the Advisory Committee itself is widely representative, not only of all sections of the country but of the major obstetrical and gynecological societies, it is believed that in a very real sense the new Editors assume their positions with the approval of the members of the specialty.

Few of our readers will need an introduction to the new Editors. Dr. John I. Brewer is Professor of Obstetrics and Gynecology at Northwestern Medical School and Chairman of the Department at the Passavant Memorial Hospital. Dr. Allan C. Barnes is Professor and Chairman of the Department at the Western Reserve Medical School. The past interest of each in the academic aspects of obstetrics and gynecology and the work of each in the elevation of the professional status of the specialty are well known.

It is inevitable that new personalities on the Editorial staff will produce changes in JOURNAL policy and outlook. This is indeed desirable and is essential if the originality and vigor of any enterprise are to be assured. However, no major changes in policy are planned for the present and any developments will be gradual.

The JOURNAL looks forward to an interesting and expanding future, which seems in general to be assured by the progress of the specialty of obstetrics and gynecology itself and, more specifically, by the editorial competence afforded by the addition of these two members to the staff.

H. C. T.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

The Premature Baby. By V. Mary Crosse. Fourth edition. 242 pages, 39 figures. Boston, 1957, Little, Brown & Company.

It is a delight to have an author describe in detail the simple and complex intricacies of the care of premature infants. Dr. Crosse does just that. In addition, she offers a very workable solution to many of these problems. Disagreements may occasionally arise between the author and the reader, such as the place of antibiotics in mild infections of the skin and polyethylene tube feedings in the larger premature infant, but these are minor differences of opinion among people caring for prematures.

The clarity with which Dr. Crosse discusses the premature infant is the outstanding virtue of this book. The writer shows that this work represents her own personal experience in the treatment of the premature and not an exhausting and unconvincing survey of the literature. It is this intimacy with the premature infant itself which recommends this book to all who are, or hope to be, caring for the premature infant.

Spontaneous and Habitual Abortion. By Carl T. Javert. 450 pages with 196 figures. New York, 1957, Blakiston Division, McGraw-Hill Book Company, Inc. $11.00.

You may not like a good deal of this book and you may disagree with many of its concepts—yet at no time will it be dull reading. The book is divided into three main sections; pathology, clinical obstetrics, and psychosomatology, with an introduction and epilogue.

The section on pathology derives most of its material from a thorough study of some 2,000 spontaneous abortions which occurred in the first two decades at the New York Lying-In Hospital. The data presented are in general agreement with what has been previously shown. Of interest is the section on cord abnormalities, the 53.7 per cent incidence of which is out of line with that given in previous studies. It contains some fine illustrations although the author's reasons for believing that these anomalies occur prior to death are not entirely convincing.

The introduction contains some good material on fertilization and placentation. The author's drawings and descriptions of placental circulation are confusing and not entirely in agreement with currently known facts and concepts. This area, however, has always been one of controversy.

It is in the sections on clinical obstetrics and psychosomatology that "freewheeling" really begins. Perhaps only two examples will serve. On page 212 there is a table said

to be the monthly variation in the incidence of abortion which indicates that "pregnancies occurring in spring and early summer had less chance of abortion than did pregnancies occurring at other times." The diets are better in summer, etc. The trouble lies in the fact that simple analysis of the table fails to show any significant monthly variation in the incidence of abortion.

In Figure 127 the author says that there is a correlation between the age of attainment of the highest frequency of orgasm and the age of highest frequency of abortion. Certainly the curves can be superimposed, rather roughly, but the conclusion is about as valid as the correlation of the high incidence of eclampsia in Arkansas and membership in the Baptist Church.

If the reaction of this reviewer is a measure of the provocative nature of the writing, then indeed the author has accomplished his purpose. It is never dull reading and interest is heightened by the delightful cartooning of Ann Ogden. Well drawn, razor-sharp, and pertinent—a little sexy at times—these cartoons add immeasurably to the text and go a long way to mitigate some of the "ascientific" flights of fancy. Only one is in poor taste. Is Figure 141 pornographic or does the reviewer have an unconscious ambivalent psychosomatic projection?

Perinatal Loss in Modern Obstetrics. By Robert E. L. Nesbitt, Jr. 432 pages, 65 tables, 108 figures. Philadelphia, 1957, F. A. Davis Company. $12.50.

What better evidence of progress in obstetrics is there than the publication of a volume of 432 pages on perinatal loss? This is preventive medicine in an area which is increasingly occupying the attention of obstetricians, pediatricians, health officers, and, indeed, the public of this country. It is timely, therefore, that what is known of this problem be set forth.

Nesbitt has brought to this work a long experience with the pathological material of abortion, stillbirths, and neonatal deaths of the Department of Obstetrics at Johns Hopkins Hospital. The thorough and efficient study and classification of all the garnered data have furnished him a background against which he is able to display good clinical judgment and practice. An omniverous reader to boot, Nesbitt has recorded an encyclopedic bibliography.

We have then no mere pathology of reproductive loss but a very thorough summation of definition, clinical basis, pathological changes, and statistical data of all the known factors of pregnancy wastage.

On occasion one feels that, with so much unknown, the author has been compelled to reach too far into clinical fields and practice. These stretchings, as only adjuncts to the main theme of the book, appear to be a bit superficial. Yet this is a new endeavor in a new field, and in the main the clinical data presented are relevant, concise, and informative.

Many of the tables are especially valuable. The photomicrographs are well reproduced and the color plates are outstanding, although the one on ruptured tubal pregnancy is apparently misplaced with those of hemolytic disease of the newborn (page 304).

Of particular interest are the chapters on anesthesia and hemolytic disease. These factors have been greatly overemphasized as they contribute to perinatal loss. The relative importance is here closely delineated.

Pathologist, clinician, bibliographer, Nesbitt approaches his last chapter on preventability with the sudden shock that with present knowledge there seems to be little that can be done to reduce reproductive wastage. It must have been a disappointment to the author to find that, at the end of as superb and complete a work as exists on the subject, he was still but a short way from the beginning.

BOOKS RECEIVED FOR REVIEW

Allergy in Pediatric Practice. By William B. Sherman and Walter R. Kessler. 296 pages, 12 figures. St. Louis, 1957, The C. V. Mosby Company. $9.25.

Inhalation Analgesia in Childbirth. By E. H. Seward. 58 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. $1.50.

A Practical Handbook of Midwifery and Gynaecology. By W. F. T. Haultain, Clifford Kennedy, and J. L. Henderson. Fifth edition. 410 pages, 48 figures. Edinburgh, 1957, E. & S. Livingstone, Ltd.

Psychological Implications of Current Pediatric Practice. 80 pages, Columbus, Ohio, 1957, Ross Laboratories.

The Reproductive Development of the Female. By M. F. Ashley Montagu. 234 pages, 4 figures. New York, 1957, Julian Press, Inc. $5.00.

El Rinon ectopico pelviano en la mujer. By M. Usandizaga. 142 pages, 28 figures. Barcelona, 1957, Vergara editorial.

Studies on Fertility. By R. G. Harrison. 138 pages. Springfield, Ill., 1957, Charles C Thomas, Publisher. $5.00.

SELECTED ABSTRACTS*

Acta obstetricia et gynecologica scandinavica

Supplement 2, Vol. 36, 1957.

*Anberg, Ake: The Ultrastructure of the Human Spermatozoon, p. 1.

Anberg: Ultrastructure of the Human Spermatozoon, p. 1.

The present study is an electron microscope investigation of human spermatozoa from sperm samples and from the epididymis, including some observations of the spermatid. The investigation has been carried out according to two different techniques, viz., ultrathin sectioning and fragmentation by means of ultrasonics.

The investigation has added some information to our knowledge of the ultrastructures of the human spermatozoon. The findings are as follows:

The *head* consists of the cell nucleus exclusively, which in its anterior tapering part is covered by a two-layered head cap. The outer and inner membranes of the cap are triple layered and parallel to each other. They are continuous with each other at the caudal end and the interspace between them is filled by a homogeneous matter. In the early spermatid the head cap is seen as a bilaminar structure, closely applied to a rather small part of the nuclear surface and with the interspace between its two membranes widened in the center to a cavity, containing a rounded, homogeneous structure. The content of the nucleus of the mature spermatozoon appears sometimes granulated, sometimes homogeneous. The nuclear membrane in the early spermatid is seen triple layered but in the late spermatid and in the mature spermatozoon it appears as a condensation of the peripheral nuclear content.

The *neck* consists of a segmented body, tapering in the caudal direction. It appears in sections as a series of transverse bands, alternating opaque and less opaque. It is concluded that the coarse fibrils of the axial filament proceed up through the peripheral part of the neck where they are segmented. They possibly end at the basal plate, a circular structure under the flattened base of the head. In the center of the proximal part of the neck there is a spherical structure, considered to be of centriolar origin. This sphere is in sections always seen to be composed of coarse opaque dots, lying in a ring around the center of very low opacity.

*Titles preceded by an asterisk are abstracted below.

The *axial filament* forms the central core of the tail and runs uninterrupted from the neck down into the end of the tail. In the whole tail it consists of two central fibrils and a surrounding tube of nine pairs of fibrils. All these twenty fibrils have a tubular appearance in cross sections. The two central fibrils are separated by an interspace but the pairs, constituting each peripheral doublet, are in close contact. Furthermore, there are interconnections between the two central fibrils and each peripheral fibril doublet. This typical 2 + 9 arrangement of fibrils, however, is sometimes broken up in the end of the tail.

In the middle piece and in the proximal part of the tail proper there is an additional tube of nine peripheral coarse fibrils, situated immediately outside and on the same radius as the corresponding fine fibril doublets. In the middle piece the coarse and the fine fibrils are separated by a narrow interspace but in the tail proper they are in close contact. The coarse fibrils are of varying thickness and homogeneous. They have an irregular cross-sectional area and taper gradually when passing down the tail, ending at different levels of the tail. The two fibrils lying opposite one another in the plane passing through the two central fibrils are always the first ones to stop. Furthermore, in the proximal part of the tail proper the peripheral fibrils, situated in the plane mentioned above, are in contact with the surrounding fibrillar sheath.

In the *middle piece* of the mature spermatozoon the axial filament is surrounded by a single layer of "vesicular" structures. By study of the development of the middle piece during the spermiogenesis and the maturing period in the epididymis it is found that these "vesicles" are highly transformed mitochondria. They are, however, not coalescing into a spiral.

In the *tail proper* there is a fibrillar sheath wrapped around the axial filament. With the preparative technique used it is impossible to determine with certainty whether this sheath is a regular helix or not. In cross sections of the tail these fibrils are seen thicker in the proximal part of the tail proper than in the distal part. Furthermore, in the proximal part they show marked thickenings, lying opposite one another in the plane passing through the two central fibrils.

In the *tail end* the axial filament is enveloped by the tail membrane.

The whole spermatozoon is enveloped by the *cell membrane* which in the tail end is observed to be triple layered.

ROBERT E. L. NESBITT, JR.

Anais brasileiros de ginecologia

Vol. 43, No. 6, 1957.

*Maretti, M., and Carvalho, N.: Test of Thyroid Function in Normal Pregnancy Using Radioactive Iodine, p. 327.

Maretti and Carvalho: Test of Thyroid Function in Normal Pregnancy Using Radioactive Iodine, p. 327.

The authors studied thyroid function in 35 apparently normal pregnant women, using radioactive iodine uptake and radioactive iodine excretion in the urine. The normal levels used for uptake were 30 per cent to 60 per cent. Normal levels in the urine were considered to be 40 per cent to 70 per cent of the ingested dose excreted. The case distributions were as follows: less than 2 months, 2 cases; 2 to 3 months, 9 cases; 3 to 4 months, 24 cases. They concluded that from the beginning until the fourth month of pregnancy, thyroid function was normal in 56.8 per cent of the cases and that hyperfunction was present in 42.6 per cent of the cases. They also concluded that normal function obtained in 11.4 per cent of the cases in the third month of pregnancy and that it was present in 17 per cent of the cases in the fourth month. They state that the normal function as evidenced by these tests is possibly due to a lack of receptivity of the fetal thyroid to iodine during the first 4 months of pregnancy.

FRANCIS B. O'BRIEN

British Medical Journal

Vol. 2, July 6, 1957.

Catterall, R. D., and Nicol, C. S.: Systemic Treatment of Trichomonal Infections, p. 29.

Catterall and Nicol: Systemic Treatment of Trichomonal Infections, p. 29.

The authors set out to test the statement that certain drugs can eradicate trichomonal infections via systemic therapy and thereby reach the organism in places inaccessible to local therapy. They tested two drugs: Trichomycin, an antibiotic isolated from Streptomyces hachijoensis and acinitrazole (2-acethyl-amido-t-nitrothiazole). Both of these drugs have high in vitro antitrichomonad effects. The first drug was tested locally, systemically, and in a combined form, with a 3 month follow-up for the local method. All patients had relapses, both male and female. Secretions, urine, and serum in selected cases were found to be lacking in antitrichomonad activity. No serious side reactions were noted. Local therapy in a group of 23 women consisted of insertion of a 50,000 unit suppository daily for 14 days; 10 women were given 5,000 unit tablets 3 times a day for 10 days; 20 women and 6 men were given up to 300,000 units daily for 2 weeks; and 4 women were given combined therapy. Acinitrazole was given to 10 women, 100 mg. 3 times a day, without success and then 9 women were given the drug orally and a suppository of phenylmercuric dinaphthylmethane disulfonate without success. The plea is made that drugs not be placed on the market until adequately tested.

FRANCIS B. O'BRIEN

Deutsche medizinische Wochenschrift

Vol. 82, 1957.

*Von Kneer, M.: Habitual Abortion, p. 1059.

*Tietze, K.: Irregular Menstrual Cycles, p. 1223.

Von Kneer: Habitual Abortion, p. 1059.

The etiology of habitual abortion is discussed in relation to the period of gestation and the appearance of the fetus. Abortion within the first 3 months is usually caused by a fetal malformation or hydatidiform mole and after that time by a uterine defect. The fetal malformation is usually caused by imperfect vascular connection between the fetus and the membranes. Development of the fetus is usually retarded while the development of the membranes is consistent with the period of amenorrhea.

Some 60 per cent of early spontaneous abortions are caused by hydatidiform moles. It is important to do a histological examination of the specimen to see the exact cause of abortion. The author emphasizes the importance of the distinction between lethal genetic factors and exogenic factors from the maternal organism, among them the lack of ribonucleic acid in the follicular epithelium. The exogenic factors may depend upon the diet of the mother, a vitamin deficiency, particularly of vitamin A, or obesity.

Abortion at the fourth to the sixth month is usually due to malformations of the uterus such as a uterus didelphys or duplex. The author recommends hysterography and operation for these cases.

CORNEL BERENKEY

Tietze: Irregular Menstrual Cycles, p. 1223.

The author gives the definition of irregularity as "the deviation in time from the average normal." Irregularities are found in most women and the prolonged cycle is usually compensated for by a shortened cycle the following month. Irregularity is thought to be dependent upon nonrhythmic influences from higher brain centers and is considered as physiologic variation. The author shows by statistics from a large series of patients that deviations and irregularities may coincide.

CORNEL BERENKEY

Wiener medizinische Wochenschrift

Vol. 106, December 1, 1956.

*Baumgartner, H., and Typl, H.: Gynecologic Bleeding, p. 1000.

Baumgartner and Typl: Gynecologic Bleeding, p. 1000.

On the basis of specific patient protocols, the authors suggest that the hemostatic agent Reptilase may have a fairly wide usefulness in both postoperative and conservative gynecologic bleeding, provided that the cases are properly selected. They state that satisfactory hemostasis was obtained by the use of Reptilase alone in several patients who prior to the introduction of this hemostatic would have been subjected to immediate operation, or alternatively to some form of tamponade or multiple transfusions. They also observed a relatively less bloody field in extensive operations such as the Wertheim and Schauta procedures, as capillary bleeding is much less prominent after administration of the drug: It is also useful in vaginal plastic operations, noticeably facilitating healing. The authors also observed some hemostatic effect in hemorrhages of hormone type. No toxic side effects or thromboembolic phenomena accompanied the use of the preparation.

DOUGLAS M. HAYNES

Vol. 107, January 5, 1957.

*Amreich, J.: The Lymph Node Problem in Operative and Irradiative Treatment of Carcinoma of the Cervix, p. 6.

Amreich: Lymph Node Problem in Operative and Irradiative Treatment of Carcinoma of the Cervix, p. 6.

In this extensive review article, Amreich reviews the embryology and anatomy of the pelvic lymph nodes, and quotes international statistics on the prognostic significance of lymph node involvement in carcinoma of the cervix. A comparison is made of the Wertheim and Schauta operations for the years 1901 to 1925 in order to demonstrate that selective excision of carcinomatous nodes does not affect the cure rate following radical operations. Evidence is cited for the uneven and inconstant growth of carcinoma cells within lymph nodes. On an anatomical basis, Amreich demonstrates that the technically infeasible extirpation of the inferior gluteal and pararectal lymph nodes would be necessary for a truly inclusive procedure for operative treatment of carcinoma of the cervix. Evidence is reviewed to show that the reticuloendothelial system is important as a body defense against cancer, and that there may be significant disadvantage to the complete removal of pelvic lymph nodes. Evidence to show that irradiation is inadequate for controlling extension to the pelvic lymph nodes is also cited.

DOUGLAS M. HAYNES

Zentralblatt für Gynäkologie

Vol. 78, December 29, 1956.

*Beck, H., and Huber, R.: Placental Permeability to Guiacol-Glycerine-Ether, p. 2053.
*Preisler, O.: Cortisone and ACTH in the Prophylaxis of Erythroblastosis, p. 2056.
Martius, G.: Histological Examination of the Placenta to Clarify the Pathogenesis of Erythroblastosis Fetalis, p. 2060.

Beck and Huber: Placental Permeability to Guiacol-Glycerine-Ether, p. 2053.

Guiacol-glycerine-ether is a skeletal muscle relaxant, working through the motor neurons of the spinal column. It does not affect the diaphragm significantly, though dyspnea is noted, caused by paralysis of the accessory muscles of respiration. The authors have found by means of the tokodynamometer that fetal movements cease when this drug is used. This leads to the conclusion that the agent crosses the placenta. Though no ill

effects have been noted until now, they feel that use of this drug may be dangerous to the baby, because it would increase the respiratory difficulties of a baby that may already be compromised. Abdominal effort during the second stage is excluded in cases where this agent is used.

WALTER F. TAUBER

Preisler: Cortisone and ACTH in Prophylaxis of Erythroblastosis Fetalis, p. 2056.

After reviewing several methods of prophylaxis against erythroblastosis fetalis which have been advocated on theoretical grounds, but found not to work when tried clinically, the author reports 2 cases in which cortisone and ACTH were used. One patient with a history of several previous deliveries, starting in the fifteenth week of pregnancy, was given 1 cm. of Depo-cortisone every 10 days. On days 7 and 9 of each cycle she received 20 units of Depo-ACTH. Titers decreased slowly from 1:256 to 1:2. No untoward side effects were encountered. A slightly edematous infant was delivered shortly before the expected date of confinement. The child required exchange transfusion and did well thereafter. The other patient was not treated until the twenty-eighth week. She was delivered of a hydropic infant who died. The author feels that failure in the second case is to be attributed to a late start in therapy. He acknowledges, however, that no definite conclusions can be drawn until his method is tried in a statistically significant number of cases.

WALTER F. TAUBER

Vol. 79, January 5, 1957.

*Döderlein, G., and Schmidt, H.: The Question of Residual Organic Damage Following Eclampsia, p. 1.

Döderlein and Schmidt: The Question of Residual Organic Damage Following Eclampsia, p. 1.

Seventeen patients with a history of eclampsia and 15 patients with previous pre-eclampsia were followed for periods up to 10 years and studies made to determine whether residual vascular, renal, or hepatic damage could be demonstrated. The conclusions drawn, based on exhaustive tests, were that simple toxemias leave no stigmas, while toxemia superimposed on pre-existing hypertension, renal disease, or liver damage may aggravate the underlying disease. It is, therefore, suggested that obstetricians and internists cooperate closely in treating pregnant women who have vascular, renal, or liver disease.

WALTER F. TAUBER

Vol. 79, March 16, 1957.

*Bakowski, E.: Urinary Fistulas Seen in the Department of Gynecology, University of Berlin, 1941-1955, p. 401.

Spurny, J.: Ureterovaginal Fistulas Following Radical Hysterectomy (Wertheim), May, 1943, to May, 1955, p. 427.

Zizlavsky, M. U.: Reimplantation of the Ureters, p. 434.

Schippel, H.: Transurethral Injection for Urinary Incontinence in Women, p. 436.

Sederl, J.: A Rare Tumor of the Bladder, p. 438.

Bakowski: Urinary Fistulas Seen in the Department of Gynecology, University of Berlin, 1941-1955, p. 401.

Fistulas seen in 293 patients in the Department were divided into 17 urethrovaginal, 19 bladder neck-vaginal, 157 vesicovaginal, 5 vesicocervical, 2 vesicocutaneous, 3 urethrotrigonal-vaginal, 22 vesicovaginorectal, 59 ureterovaginal, 4 ureterocervical, 3 ureterovaginocutaneous, and 2 ureterovaginorectal. It was noted that the urinary tract was injured 1.1 per cent of the time, in about 16,500 gynecologic operations. If the injury was

recognized and repaired, sequelae were rare (0.2 per cent) even though most of the difficulties occurred in Wertheim operations. Surgical difficulty, injury in childbirth, and spontaneous malignant fistulas contributed to 76 cases diagnosed at the clinic. The remainder were referred to the University from elsewhere.

Of the 293 cases, 63, 22 per cent, were not amenable to therapy; 89 per cent of the other 230 were cured by operation. The failure rate was 4 per cent; the mortality rate 7 per cent.

WALTER F. TAUBER

Vol. 79, March 23, 1957.

Niedner, K.: New Methods for Collecting Menstrual Blood for Diagnosis With the "Hemotophor," p. 449.

Buessing, H. J.: Biochemistry of Menstrual Blood, p. 456.

Otto, K.: The Occurrence and Etiology of Adenomyosis Interna. A Report on Two Atypical Cases, p. 471.

Irmscher, A.: Total Protein and Polarographic Reaction of Serum in the Menstrual Cycle and Early Pregnancy, p. 480.

Stoecker, E., and Sievert, C.: Capillary Angioma of an Endometrial Polyp, p. 484.

Vol. 79, March 30, 1957.

*Kraussold, E.: Incidence and Results of Treatment of Carcinoma of the Cervical Stump at the University of Berlin, 1938-1950, p. 497.

*Lewin, E.: Rare Cases of Metastasis to the Female Genital Tract—Four Cases, p. 510.

Ganse, R.: Atypical Neovascularization With Carcinoma, p. 519.

Orts, L.: On the Question of Malignancy of Granulosa Cell Tumors. A Case Report, p. 524.

Kraussold: Incidence and Results of Treatment of Carcinoma of the Cervical Stump at the University of Berlin, 1938-1950, p. 497.

Between 1938 and 1950, 77 cases of carcinoma of the cervical stump were observed at the University of Berlin. Eight of these occurred within one year of supracervical hysterectomy. The author feels that in these cases the lesions must have been present prior to operation. The remaining 69 cases of "true" stump carcinoma represent 2.05 per cent of the cases of carcinoma of the cervix (3,356) seen at the clinic. No statistically significant rise has been observed in the incidence of carcinoma of the cervical stump over the years covered by the study. The average age of the patients was 51.8 years, compared to 45 to 50 for all patients with carcinoma of the cervix. The over-all cure rate was 40.5 per cent for true stump carcinoma, with a 60.6 per cent rate for the surgical and 22.2 per cent rate for the radiation patients. The prognosis for carcinoma of the stump is no worse than for other cervical carcinomas. However, these patients fare comparatively worse if the lesion is in Stage III or IV and better if it falls into Stage I or II. Supracervical hysterectomy should generally not be used on patients who are over 40 years old or who have any suspicious lesion of the cervix. Patients who had such an operation should be followed closely for the rest of their lives.

WALTER F. TAUBER

Lewin: Rare Cases of Metastasis to the Female Genital Tract—Four Cases, p. 510.

Four cases of malignancy metastatic to the female genital tract are reported, namely: a melanosarcoma of the skin, metastasizing to the ovary; an epipharyngeal sarcoma found in the ovary; a carcinoma of the colon found in the cervix; and a bronchiogenic carcinoma with metastases in the vulva.

WALTER F. TAUBER

Items

"The Foundation Prize" of the American Association of Obstetricians and Gynecologists

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Manuscripts must be presented under a nom de plume, which shall in no way indicate the author's identity, to the President of the Foundation, together with a sealed envelope bearing the nom de plume and containing a card showing the name and address of the contestant.

Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

Three copies of all manuscripts and illustrations entered in a given year must be in the hands of Jean Paul Pratt, M.D., Henry Ford Hospital, Detroit, Michigan, President of the Foundation, before April 1, 1958.

Inquiries for further details should be addressed to the Secretary, E. Stewart Taylor, M.D., University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, Colorado.

Mathieu Memorial Chorionepithelioma Registry

Dr. John I. Brewer has been appointed Chairman of the Mathieu Memorial Chorionepithelioma Registry of the American Association of Obstetricians and Gynecologists to succeed the late Dr. Emil Novak. Specimens should now be sent to Dr. Brewer, Department of Obstetrics and Gynecology, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11, Illinois.

American Board of Obstetrics and Gynecology

The next scheduled examinations (Part II), oral and clinical for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 7 through 17, 1958. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible.

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A brief chapter on normal labor and another concerning the normal puerperium as a basis for the discussion of the management of complicated delivery and of postpartum disorders have been added. The changes which occur in the maternal organism in response to pregnancy are not consolidated in a separate section but are considered as they relate to and influence each of the complications. In some instances the material was rearranged to permit a single complete discussion of certain conditions rather than to describe their treatment during pregnancy, labor and the puerperium separately; the management of the third stage of labor and the treatment of postpartum hemorrhage, for instance, are considered together, and breech delivery is combined with version and breech extraction which are similar in many respects. The portions of the book on erythroblastosis fetalis and the examination and care of the newborn infant were prepared by Dr. Victor C. Vaughan, III, Assistant Professor of Pediatrics in the Temple University School of Medicine.

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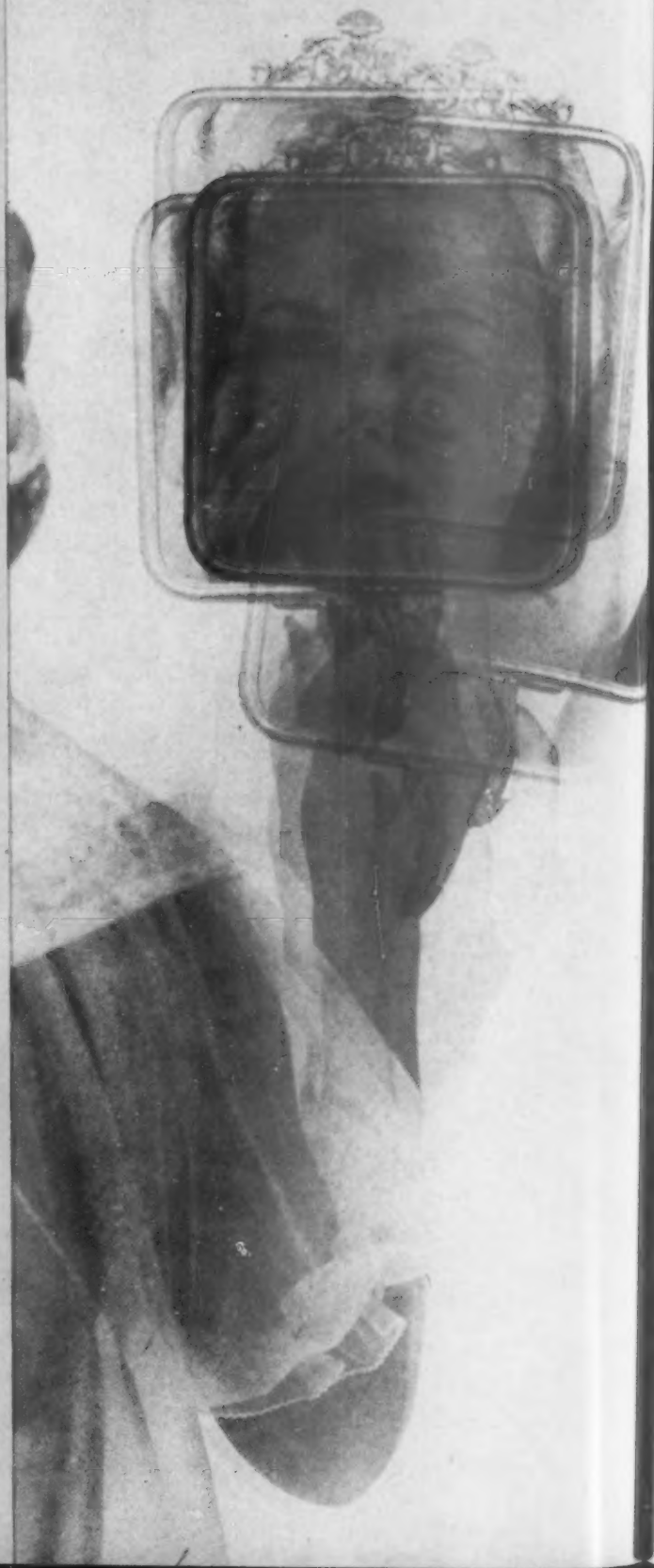

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Vol. XXVII, Fasc. II **February, 1958**

CONTENTS

Berg, O. A.: The normal prostate gland of the dog ---------- 129

Berg, O. A.: Parenchymatous hypertrophy of the canine prostate gland ---------- 140

Berg, O. A.: Effect of stilboestrol on the prostate gland in normal puppies and adult dogs 155

Pesonen, S., and Mikkonen, R.: Observations on the significance of dehydroepiandrosterone, androsterone and etiocholanolone determinations in the differential diagnosis of certain adrenal and ovarian diseases ---------- 170

Connell, A. M., Cooper, J., and Redfearn, J. W.: The contrasting effects of emotional tension and physical exercise on the excretion of 17-ketogenic steroids and 17-ketosteroids ---------- 179

Berezin, D., Genell, S., Møgelvang, M., and Staland, B.: On the use of methylandrostenediol in gynecology ---------- 195

Friis, T., and Chapman, E. M.: The function of the thyroid in euthyroid patients with exophthalmos ---------- 207

Roy, S. N., Karkun, J. N., and Sur, R. N.: Changes in the adrenal of hypothyroid (thiourea-induced) rats and the influence of testosterone propionate on such changes 216

Suchowsky, G.: Der Einfluss von Sexualhormonen auf die Nebennieren der Ratte ------ 225

Pyörälä, K.: Effect of digitoxin and k-strophantin on the adrenals and testes of the guinea-pig ---------- 238

von Studnitz, W., and Berezin, D.: Studies on serum copper during pregnancy, during the menstrual cycle, and after the administration of oestrogens ---------- 245

Ramaswami, L. S., and Sundararaj, B. I.: Action of enzymes on the gonadotrophic activity of pituitary extracts of the Indian catfish Heteropneustes ---------- 253

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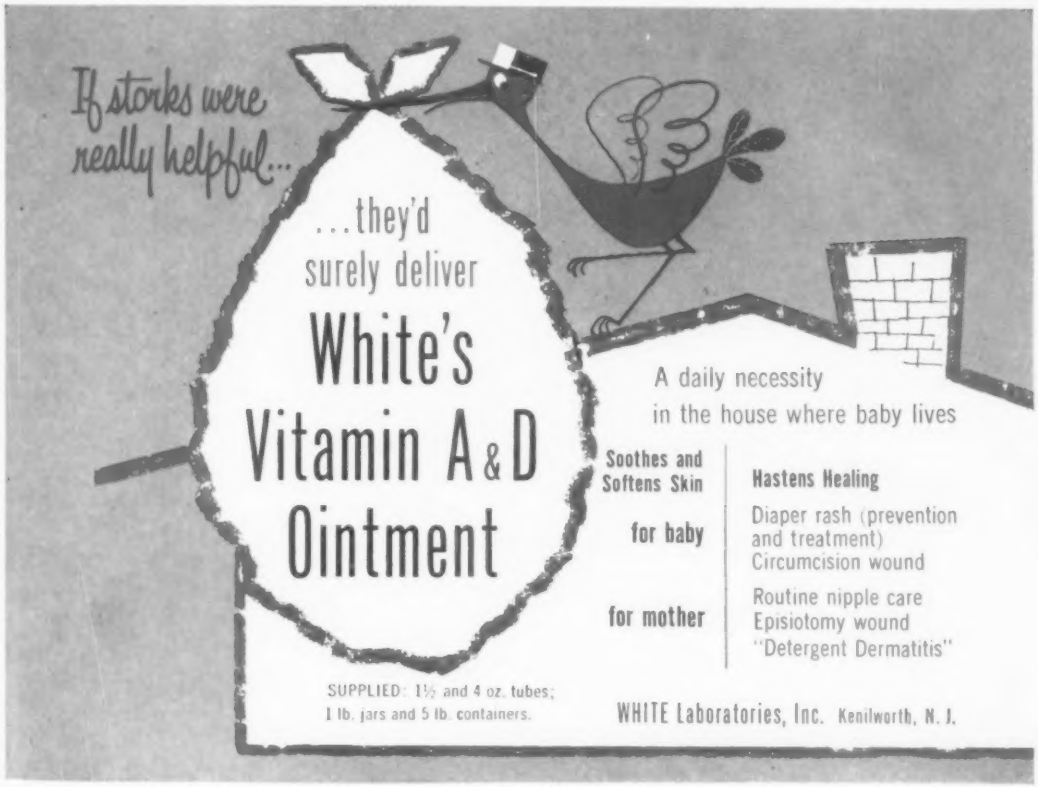
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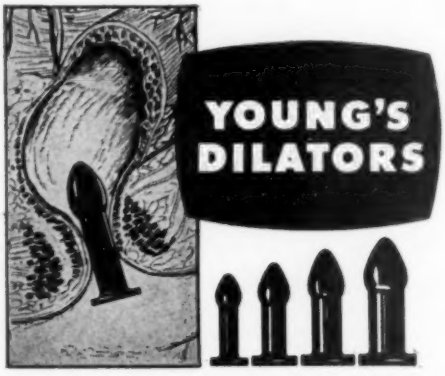

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Ayerst Laboratories ---------- 49

Baxter Laboratories, Inc. ---------- 78
Birtcher Corporation, The ---------- 71
Borden Company, The ---------- Fourth Cover
Brayten Pharmaceutical Company ---- 60
Bristol Laboratories, Inc. ---------- 28, 29
Bristol Laboratories, Inc. ----------
---------- Insert between pp. 48 and 49
Burroughs Wellcome & Company (U. S. A.), Inc. ---------- 22

Caduceus Press ---------- 92
Carnation Company & Subsidiaries ---- 40
Ciba Pharmaceutical Products, Inc. ----------
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Desitin Chemical Company ---------- 30
Doho Chemical Corporation ---------- 30
Dome Chemicals, Inc. ---------- 69

Eaton Laboratories ---------- 19, 34, 35
Elder Company, Paul B. ---------- 92
Esta Medical Laboratories, Inc. ---------- 61
Ethicon, Inc. - Insert between pp. 16 and 17

Fesler Company, Inc., The ---------- 47, 48
Florida Citrus Commission ---------- 87
Fougher & Company, Inc., E. ---------- 27

Grant Chemical Company, Inc. ---------- 72

Holland-Rantos Company ---------- 10, 63

Johnson & Johnson ---------- 37

Lakeside Laboratories ---------- 17
Lederle Laboratories ---------- 53, 65
Lilly and Company, Eli ---------- 84
Lloyd Brothers, Inc. ---------- 55

Massengill Company, The S. E. ----------
---------- Insert between pp. 24 and 25
Massengill Company, The S. E. ----------
---------- Insert between pp. 32 and 33
Massengill Company, The S. E. ----------
---------- Insert between pp. 40 and 41
Merck Sharp & Dohme ------ 24, 54, 56, 57
Merrell Company, The Wm. S. ------ 15, 64

National Drug Company, The ----------
---------- 12, 32, 50, 51

Organon, Inc. ---------- 5
Ortho Pharmaceutical Corporation ----
---------- 33, 39, 59, 67

Pet Milk Company ---------- 52
Pfizer Laboratories, Div. Chas. Pfizer & Company, Inc. ---------- 42, 64a
Poythress & Company, Inc., Wm. P. --- 77

Quaker Oats Company, The ---------- 18

Riker Laboratories ---------- 16
Robins Company, Inc., A. H. ------ 20, 21
Roche Laboratories, Div. of Hoffmann-La Roche, Inc. ----------
---------- Insert between pp. 64 and 65
Roche Laboratories, Div. of Hoffmann-La Roche, Inc. ---------- 80
Roussel Corporation ---------- 23

Schmid, Inc., Julius ---------- 79
Searle & Company, G. D. ---------- 9, 85
Sklar Manufacturing Company, J. ----- 44
Smith, Kline & French Laboratories --
---------- 3, 25, 41, 58, 82
Squibb & Sons, E. R. ---------- 43, 62, 73
Stuart Company, The ---------- 88

Tampax Incorporated ---------- 81

Walker Laboratories, Inc. ---------- 96
Wallace Laboratories ----------
---------- Insert between pp. 36 and 37
Warner-Chilcott ---------- 7, 26, 66
Webster Company, The William A. ----
---------- Third Cover
Westwood Pharmaceuticals ---------- 83
White Laboratories, Inc. ---------- 11, 89, 93
Whittaker Laboratories ---------- 86
Williams & Wilkins Company ---------- 70
Winthrop Laboratories ---------- 14
Wyeth Laboratories ---- 31, 38, 75, and 91

Young and Company, F. E. ---------- 92

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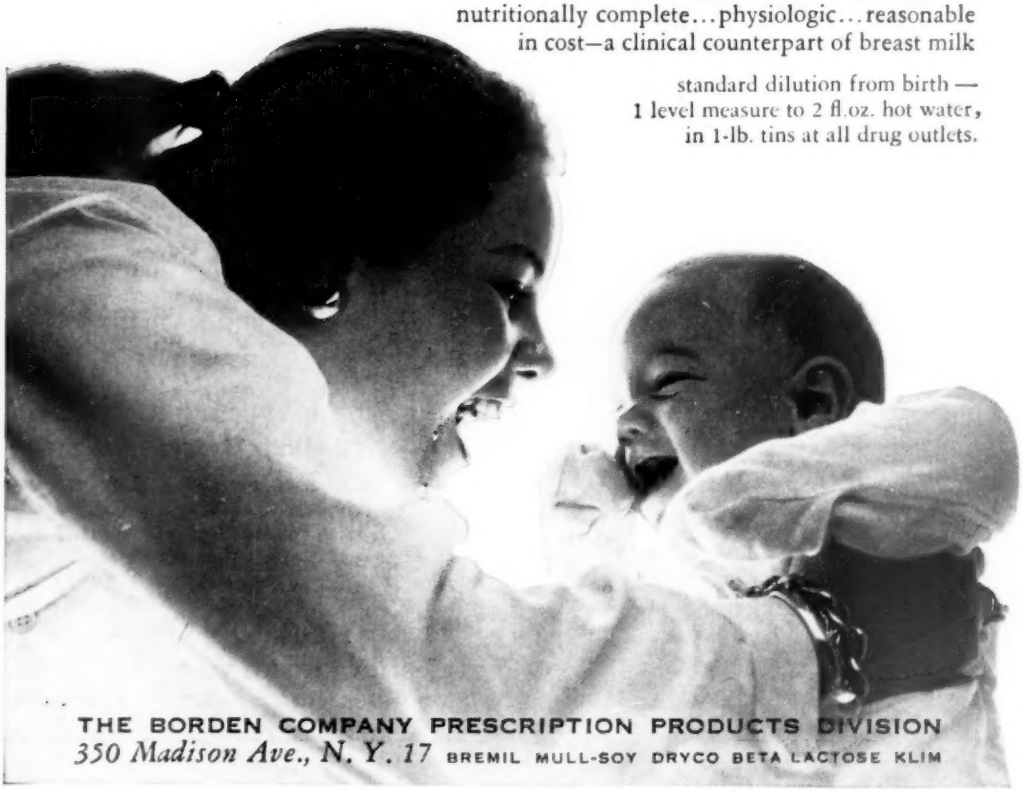

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